ACTA PÆDIATRICA

REDACTORES:

A. LICHTENSTEIN, STOCKHOLM, A. WALLGREN, STOCKHOLM

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IN DANIA: BENT ANDERSEN, AARHUS, OLUF ANDERSEN, KØBENHAVN, C. E. BLOCH, KØBENHAVN, P. PLUM, KØBENHAVN. IN FENNIA: P. HEINIÖ, HELSINGFORS, V. RANTASALO, HELSINGFORS, C.-E. RÄIHÄ, HELSINGFORS, T. SALMI, ÅBO, ARVO YLPPÖ, HELSINGFORS. IN HOLLANDIA: E. GORTER, LEIDEN, CORNELLA DE LANGE, AMSTERDAM, J. VAN LOOKEREN CAMPAGNE, GBONINGEN. IN NORVEGIA: TH. FRÖLICH, OSLO, LEIF SALOMONSEN, OSLO, L. STOLTENBERG, OSLO, A. SUNDAL, OSLO, KIRSTEN UTHEIMTOVERUD, OSLO. IN SUECIA: C. GYLLENSWÄRD, UPPSALA, N. MALMBERG, STOCKHOLM, STURE SIWE, LUND, WILHELM WERNSTEDT, STOCKHOLM, Y. ÅKERRÉN, GÖTEBORG.

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A C T A P Æ D I A T R I C A

PROFESSOR A. LICHTENSTEIN KRONPRINSESSAN LOVISAS BARNSJUKHUS, 30 POLHEMSGATAN, STOCKHOLM

The 'ACTA PÆDIATRICA' contain articles relating to pediatrics. These articles are published in English, French or German, according to the wishes of the author. Each number consists of about 6 printed sheets, 4 numbers forming a volume. The numbers will be issued as soon as the articles sent in can be printed. The 'Acta' is open to articles from foreign authors in all countries, if sufficient space can be found for them. Manuscripts are to be sent direct to the Editor, to whom also enquiries about the exchanging of papers are to be directed. The subscription should be forwarded to the Editor. Each volume costs 25 Swedish crowns or 25 shillings or 5 dollars.

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A CTA PÆDIATRICA





medical, direct

FROM THE CHILDREN'S HOSPITAL "LASTENLINNA", HELSINKI, PRINCIPAL: PROFESSOR ARVO YLPPÖ. FROM THE PATHOLOGICAL INSTITUTE OF THE UNIVERSITY, HELSINKI, PRINCIPAL: PROFESSOR ARNO SAXEN.

A Case of Tuberose Sclerosis.

By

SAKARI LAHDENSUU.

Tuberose sclerosis is a very uncommon disease. According to HOJER-PEDERSEN only about 400 cases are recorded in the medical literature of the whole world. In Denmark the number of recorded cases of tuberose sclerosis is 17. In Finland Geitlin described (1905) one case in detail paying special attention to the pathological-anatomical and histopathological aspects of the disease. — The first case of tuberose sclerosis was described by von Recklinghausen, the investigator of the wellknown neurofibromatosis-disease. He demonstrated a newborn, establishing myoms in its heart and several sclerotic areas in its brains. The study of this disease was later developed by various observers, e.g. Bourneville, Pringle, Bielschowsky, Gallus, JOSEPHY, AMMERBACHER, DALSGAARD-NIELSEN, HOJER-PEDER-SEN etc. Thus was formed the clinical picture of tuberose sclerosis by which is understood a disease involving greater and smaller tubers and indurations in the central nervous system, above all in the cerebrum but often also on the skin (adenoma sebaceum) and occasionally even on the mucous membranes (papillae). Sometimes there is evidence of tumours in the kidneys, in the heart and in the retina. Clinically the main symptoms are: convulsions, imbecility or a gradually developing idiocy (at the beginning sometimes only a inferioritas intellectualis or debilitas mentis is identified) and dermatic changes. The disease begins usually during the infancy but primary symptoms are often reported immediately after the birth. Epileptiform convulsions

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are the first as well as the most frequent symptoms (about 80 % of the cases). Its clinical aspects may vary considerably. Epilepsy, mental disturbances and infections can occur either alone or together. In most cases these symptoms are present simultaneously but usually naevus sebaceus or acedoma sebaceum does not appear among them before the age of ten, occurring occasionally even as late as at the age of puberty. One of the symptoms may be lacking and sometimes again only one of the above incidences be present. In this case the diagnosis can generally be formed only by resorting to post mortem examination.

Tuberose sclerosis is diagnostically almost non-existent in Finland the disease being as uncommon here as anywhere else. I have therefore considered it well justifiable to describe it in the first place on the basis of a case treated in »Lastenlinna».

The case under survey: A child, born June 10, 1943, weight 3 kg. Normal delivery, 4th child. Admitted to *Lastenlinna* on November 5, 1943 on account of vomiting, recurring stomach trouble, light, restless sleep and slow physical development. (The patient weighed only $4^{1}/_{2}$ kg on the day of admittance, the increase in her weight being thus not more than $1^{1}/_{2}$ kg in five months.)

Anamnesis: The parents did not know the distant family history but as far as they were informed there was no evidence of either imbecility, insanity, nervous diseases and epilepsy or physical deformities, visual disturbances or any particular eczemas. One of the father's sisters died young of convulsions and two other sisters of some »children's diseases». - The total number of children in the family was five and there had been one miscarriage. The eldest child (six years and a half) and the youngest (ten months) alive, three daughters between these two had died. The eldest of the daughters died of convulsions and asthma at the age of a year and nine months according to the district physician's certificate. Before that she had developed well and been a strong child. — The next daughter died at the age of three and the course of her illness resembled that of the case under survey so that it is perhaps necessary to describe it here in some detail. This daughter was born about a month prematurely, her birthweight being 3 kg. She grew up slowly, ate little and vomited from time to time. A little before her first year the vomiting increased during a few weeks and the child threw up even the water. When 12 months old she weighed only 8 kg. Then the vomiting stopped automatically occurring only now and then. The child's appetite was never a good one. When she reached

the age of two the vomiting increased again being, however, followed by a better phase when she threw up only occasionally. 5—6 months later there was evidence of some kind of disturbances of consciousness. After about 2—3 months the child suffered again from convulsions and diarrhoea which had been recurring from time to time during her whole life. There was a rise in the temperature up to 41° C and the child was unconscious. After this she remained weak: some days were a little better but these were followed by bad periods when she slept from morning to night. Vomiting recurred again. About a week's time before her death she was alternately conscious and unconscious and suffered from convulsions. The death certificate stated »brainfever» as the cause of her death. According to the mother the child's general development was very slow: she began to walk at the age of 16 months but did not learn to talk until six months later. She was on the whole a delicate child and of small size.

After her birth the child under survey here had a bad colour. When two days old she was about to die having several convulsions, but survived and developed normally for about six weeks vomiting, however, every now and then. After that she stopped increasing in weight and

was brought to »Lastenlinna» for medical treatment.

Status praesens (November 6, 1943): A weak-looking child. Weight $4^{1/2}$ kg, height 60 cm. Skull measurement 40 cm. Chest measurement 35 cm. Lifted her head a little but looked tired. Complexion healthy but pale. Eyes and ears in good condition. Throat and mouth: nothing to report. The tension of the fontanelle normal, no stiffness either in the body or in the extremities. Reflection normal. Bones: 0. Heart and lungs: nothing to report. Stomach big and dilated (meteorism). Liver normal, spleen enlarged (very clearly noticeable below the arcus costarum). Vomiting. Excrements normal. Urine: turbid, albumin +, Nylander -, sediment 0. Pirquet -, haemoglobin 56/69. Wassermann reaction -.

Decursus morbi: Broadly speaking the child had always a retarded development with the exception of 3—4 months which showed some improvement. She was on the whole very sickly being over a year under medical treatment. Vomiting occurred frequently, being sometimes very intense and of long duration. There were also occasional symptoms of diarrhoea and the appetite was generally very poor. Almost constant albuminurine, only rare intervals without any albumincontent. No "cylinders" and blood in the urine. Retarded mental development. At the beginning the child sometimes smiled and prattled, tried to lift her head but learnt never to sit and keep her legs. When 12 months old she began to turn to her side but later on even this ability disappeared. She was drowsy and tired, sometimes again irritable and freful and her sleep was restless. When she was a little over a year she

began to observe her surroundings but some 2-3 months before her death she took no more any notice of her neighbourhood, her eyes were wandering and she made rather a stupid impression. When she was ten months old she suffered from spasms, was sometimes unconscious and vomited frequently. The vomiting continued for about a week but the spasms and the intermittent unconsciousness over two weeks. Neckpuncture: the fluid clear, Pandy and Nonne negative, the pressure raised. This was followed by a period of about three months of comparative health. When the child was 14 months old the intense vomiting recurred again though the stomach was otherwise in good condition. This went on for a couple of weeks and was followed by severe convulsions during two days, one fit lasting about eight hours. After this the child was unconscious 48 hours. Unconsciousness occurred at times during several days and afterwards there was occasional very serious restlessness of long duration. It was gradually observed that the child began to have subnormal temperature which was very difficult to get up even with hot water bottles. A few weeks before her death the temperature curve showed great rises and falls and the child began to vomit intensely. Her general condition was poor and she was very tired and dull. The pressure of the fontanelle was normal and there was no stiffness in the neck. Owing to the patient's condition a lumbar puncture was undertaken: the pressure was normal, the fluid turbid, Pandy and Nonne slightly positive, some leucocytes and basilli in the sediment staining. Three days later the temperature went up again and the child had convulsions. Excessive vomits occurred and on the following day exitus letalis. - Further particulars about the physical growth of the child: Increase in weight during a period of more than a year only 1 1/2 kg, increase in height only from 60 to 66 cm, chest measurement from 35 to 40.5 cm and skull measurement only from 40 to 42.5 cm.

Post mortem examination (the author): The cranium of weak construction. When opening the skull ample secretion of yellow fluid. Brains at several points grown fast to the inner surface of the skull-cap. These adherent points fairly easy to separate. On the surface of the brains abundant jelly-like exudation with plenty of fine blood-vessel fascicules shining through. At some points bigger purplish patches on the surface of the brains (haemorrhages). Also inside the skull-cap abundant accumulation of yellowish, jelly-like deposition and below it in the occipital region some greater and a few smaller haemorrhages. Inside the cranium plenty of yellowish fluid. Layers of yellow jelly also on the lower surface of the brains. Hard tubers of the size of a bean or a pea recognizable in the cerebral region at the examination of cerebral surfaces. These tubers and indurations stand out clearly against the surrounding cerebral tissue as somewhat lighter spots. Some of these formations resemble hardened parts of gyruses while the others are rounded,

navel-like and encircled by a groove or a furrow. The rounded tuber resembling the half of a bean is easily distinguishable in these standing out against its surroundings. The consistence of both of these types and especially of the latter is almost cartilaginous which can be verified when cutting open the tuber. The normal difference between the white and grey matter on the cut surface is not recognizable at the site of the indurations. We pass ambiguously from the layer of the grey matter to the white without any definite boundary. On the cut surface the consistence of these formations is similar to that on the hemisperal surfaces. In addition to the convexity these indurations and tubers appear also on the basal and medial surfaces. They are evenly positioned all over the surfaces without any marked predisposition. — The hemispheres are symmetrical and no special characteristics can be perceived either in their size or in their form. When the lateral ventricles are opened they are found to be somewhat enlarged and containing plenty of dirty grey fluid. Indurations of different shapes standing out against the surface are found also on the walls of the ventricles. Some of them are as large as the half of a bullet while the others are tubers of the size of a barleycorn. Their consistence resembles that of the hemispherical tubers. — These tuber formations are not encountered on the surface of the cerebellum.

As a serious oversight is to be mentioned that only the skull and the brains were opened at the post mortem examination. The presence of renal tumours might — upon later consideration — have been probable in this case owing to the almost continuous prevalence of albuminuria. According to literature albuminuria has been established only in a few cases (1—2 %), whereas renal tumours have been met in about 30—50 % of the cases.

 $Diagnosis\ of\ the\ post\ morten\ examination:$ Tuberose sclerosis. Meningitis purulenta.

The unusually large exceptional cells are the most striking feature in the constitution of these tubers from the microscopical point of view. They are polymorphous, monstrous cells, rich in protoplasma which is usually homogenous. As to their composition they chiefly resemble gliacells, most of them astrocytes. The nuclei which generally have several nucleoles are large and placed eccentrically. Cells with two nuclei and those in the process of splitting are often met with. The margins of many cells are at some places uneven and they have longer and shorter prolongations tapering towards the points. These are the beginnings of gliafibres. These monstrous astrocytes are sometimes

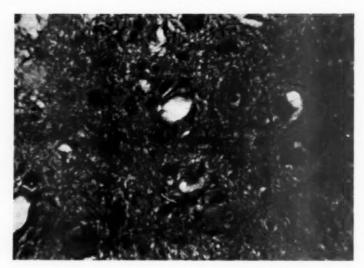


Fig. 1. v. Fieandt gliastaining $(400 \times)$. Some monstrous large cells. Plenty of gliafibres.

rounded and unusually large. Gliacells and gliafibres have increased in these tubers almost without an exception. Fig. 1, which has been stained using the v. Fieandt method of gliastaining, illustrates some of these large cells. The great number of gliafibres is also worth special attention. These actual tubers present also many calcareous concretions. At some places they are found in abundance while the others have no trace of them. Some tubers present no evidence of them at all. These calcareous concretions are smaller than the exceptional cells. A lighter spot can sometimes be discerned inside the concrement and in the spot nuclear deposit with nuclei. There is no cerebral accumulation in the tubers, the different layers are intermixed and at all events without a definite boundary. (Fig. 2 shows 7—8 calcifications and (in the left upper corner) three astrocytic cells with their long extensions.)

The different cerebral strata are fairly distinctly recognizable in some other brain tumours, i.e. in the so-called hypertrophic

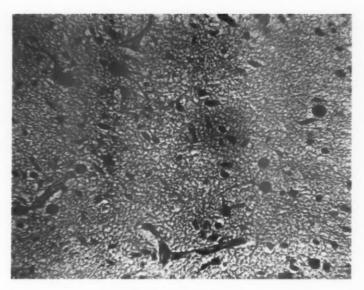


Fig. 2. v. Giesson staining (180 ×). Several calcareous concretions, Astrocytic cells with their appendices (in the left upper corner).

gyruses. Glial tissue has also increased in these, the stratum zonal particularly presenting a large network of irregularly interlaced gliafibres which often appear in thick or thin clusters. Lamina pyramidalis contains also plenty of fibrous glia but compared with the former already more scantily. The astrocyte formations of the cells are not so abundant in the more superficial strata and they are also smaller. In the deeper layers their number is greater and they increase in size being on the borderland of the white matter large, rich in plasma and with several nuclei as described above.

Similar changes are visible in the tumours on the side of the ventricles: large cells rich in plasma with enormous nuclei, resembling in the first place hyperplastic astrocytes, as well as a great number of narrow fusiform cells in the layers immediately below the ependym.

The above clinical picture of the disease involving as its main symptoms epileptiform convulsions, slow mental and physical development (mentally the child gradually degenerates from debility to complete idiocy), almost constant albuminuria and changes in the cerebrum identified at the post mortem examination as well as histo-pathologically doubtlessly justifies the presentation of the diagnosis of tuberose sclerosis. This diagnosis can very often be determined already on the basis of the macroscopical examination as the exterior appearance and the palpitation of the cerebrum give a very characteristic picture. The gyruses on the cerebral surfaces display somewhat hardened and enlarged areas and cartilaginous tubers encircled by a ringshaped groove. These are recognized very distinctly at the examination of the cerebral surface. In the case under survey I could immediately divine when examining the surface of the brains that some special brain disease was involved. - Microscopically the clinical picture of the disease is very clear and typical. In the tubers and hypertrophic gyruses in the cortex the cells have increased to a great extent and there is a considerable amount of voluminous cells with very homogenous plasma and large nuclei. At the margins of the cells there are some prolongations, the beginnings of gliafibres. These have generally increased and those numerous exceptional large cells are in the first place monstrous cellformations belonging to the gliatissue. They have sometimes two, sometimes again, though more rarely, three nuclei. In the deeper parts of the tuberose indurations there are calcareous concretions some of which present evidence of some matter resembling the remains of cellstructure. And as we notice, moreover, that at points where the calcifications are more abundant there are none of these »large cells» we can assume that these cells gradually degenerate in an increasing degree, alter and calcify finally. Literature suggests that the calcifications, especially those in the ventricular tumours can grow so large that they are visible even to x-ray (MARCUS, DALSGAARD-NIEL-SEN etc.). - In the case reviewed here the cerebral tumours greatly resemble a multiform glioma or astrocytoma. According to literature there is a close resemblance between the cerebral

indurations, characteristic of the disease, and the tumours of the gliomagroup. In Bielschowsky's opinion they resemble most a ganglioglioneuroma. In the case reported by Hojer-Peder-SEN it has been microscopically verified as a gliablastoma with large cells. Histopathologically no scientist has identified any inflammatory symptoms and Bielschowsky has proved that we have here a case of the excessive growth of blastomatic glia and some kind of hybrid between deformation and neoplasma. Peculiar and diagnostically very interesting is the presence of various tumourformations in many other organs. Renal tumours are mostly multiple, subcapsular, they can project from the surface of the kidney and be grown fast to the kidneycapsule. Microscopically they are hybrid tumours: fibromyoms, lipomyoms, angiofibromata etc. At a more advanced age the renal tumours sometimes grow so large that they cause death in the form of uraemia. — Heart tumours too are usually multiple. In most cases they have been identified as rhabdomyoms, rhabdomyolipoms and rhabdoleiomyoms. - Retina tumours are fungous tumours. They are generally identified as gliomas. Cells of the type of gangliacells are not often found in them. — Skin tumours are very typical of the disease, the most characteristic being adenoma sebaceum or naevus sebaceus (type Pringle). Generally, these are fairly symmetrically situated in the nasal region and in the nasolabial plica. Their colour is either reddish yellow or deep red. Skin tumours are sometimes similar to those met with in neurofibromatosis (called the disease of Reckling-HAUSEN). In the case under survey here there were no skin tumours and it has been ascertained that they occur usually only after the tenth year or not until the age of puberty.

Actiologically the disease is now considered to be caused by endogenous factors and to be hereditary. Many familial hereditary cases have been published in recent years. Several more or less abortive forms have been noted which it has been possible to trace for more than 2—3 generations. The form of the heredity has not been strictly defined. In some cases it seems to be dominating, in others again vaguely dominating and in several recessive. Various hereditary mutation factors play undoubtedly

an important part in the lineal descent of this disease. The anamnesis of the case of tuberose sclerosis under survey here reveals many phenomena which suggest the degeneration of the family. According to the anamnesis one of the patient's sisters had a very similar illness and it is also worth mentioning in this connection that three of the family's five children have died besides which there has been one miscarriage.

In the clinical picture given above both the anamnesis and the investigations and observations made in connection with it as well as the macroscopical and microscopical examinations of the cerebrum are thoroughly characteristic of tuberose sclerosis. In addition to this the information provided by the anamnesis proves and supports the conviction of the hereditary nature of this disease.

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Freie Kost bei Diabetes mellitus bei Kindern.

Erfahrungen aus 10 Jahren in Finnland.

Von

PER FORSSELL.

Einleitung.

Im Jahre 1935 veröffentlichte ich die Resultate einer Nachuntersuchung von Kindern, welche in den 20 Jahren von 1914—1933 in der Kinderklinik der Universität Helsingfors wegen Diabetes mellitus behandelt worden waren. Die Anzahl der Patienten in diesem Zeitabschnitt machte 181 aus; davon waren 162 nach dem Jahre 1922 in das Krankenhaus aufgenommen worden, in welchem Jahr das Insulin erfunden wurde. Über diese Letzteren konnten in 123 Fällen Angaben erhalten werden, wonach von ihnen 78 gestorben waren. Die meisten waren schon im ersten oder zweiten Jahr der Krankheit gestorben. Die Todesursache war in den meisten Fällen unkompliziertes Coma diabeticum. Die Prognose war also sehr düster, und das Resultat der Behandlung war schlechter als in irgendwelchen anderen Ländern, von welchen uns statistische Angaben zur Verfügung standen.

Im Zusammenhang mit der Diskussion darüber, was zur Verbesserung der schlechten Prognose getan werden könnte, brachte ich die Vermutung vor, dass die Behandlungsform mit freigewählter Kost, die von dem Breslauer Paediatriker Stolte im Jahre 1931 eingeführt worden war, sich eventuell als für die finnischen Verhältnisse besonders geeignet erweisen könnte. Von dieser Therapieform konnte man gute Resultate erwarten im

Hinblick darauf, dass die absolute Mehrzahl der Patienten auf dem Lande wohnte, wo der in vielen Fällen lange Weg zum nächsten Arzt und Krankenhaus sowie schlechte ökonomische Verhältnisse die Überwachung des Gesundheitszustands der Kinder und die Durchführung der Behandlung erschwerten.

Nachdem Stolte im Jahre 1931 seine ausserordentlich positiven Erfahrungen in einer Reihe von Fällen publiziert hatte. haben zahlreiche Autoren (Söderling, Lichtenstein, Hirsch-KAUFMANN, SCHEMMEL, RÄIHÄ, VEGTER, BOJLÉN u. a. m.) sich einstimmig gut in der gleichen Richtung ausgesprochen. Die Vorteile einer frei gewählten Kost schienen offenbar zu sein. Die Kinder brauchen kein sozusagen »rationiertes» Dasein zu führen, sie dürfen in normaler Weise ihren Hunger befriedigen, und sie befinden sich nicht mehr in einer Ausnahmestellung, die im Hinblick auf ihre psychische Entwicklung alles andere als vorteilhaft ist. Sie entwickeln sich normal sowohl physisch als auch psychisch und überstehen akute Infektionskrankheiten recht gut. Trotz der vermehrten Zufuhr von Kohlehydraten brauchte die Insulinmenge in vielen Fällen nicht erhöht zu werden, sondern man konnte sie im Gegenteil vermindern; auf jeden Fall ist der Insulinbedarf nicht proportional mit der Kohlehydratzufuhr gestiegen. Die Wirkung auf das Vorkommen von Acetonämie ist günstig gewesen; Koma und Präkoma kamen seltener vor. Desgleichen sind die Gefahren des Auftretens von Hypoglykämie geringer geworden.

Manche Forscher, u. a. Wallgren, Herlitz, Kirsten, Utheim Toverud (Aussprache auf dem Nordischen Paed. Kongress in Oslo 1938) sind nicht geneigt, die »freie Diät» vorbehaltslos anzuwenden, sondern sie verordnen eine in gewissem Umfang beschränkte Zufuhr von Kohlehydraten. Dieser Auffassung schliesst sich auch Müller an, nach dessen Ansicht eine freie Kost wegen der schweren Insulinanpassung nicht ohne Gefahren ist. Stolte betont indessen ausdrücklich, dass er mit freier Kost keine zügellose Verabreichung von Süssigkeiten meint, sondern nur eine freie »durch den Instinkt bedingte Ergänzung und Begrenzung der Nahrung». Die freigewählte Kost bei Kinderdiabetes ist immer noch nicht überall gutgeheissen

worden. Eine Autorität wie der Österreicher Priesel erklärte sich im Jahre 1941 als der Anhänger einer kombinierten Insulinund Diätbehandlung. Er ist der Ansicht, dass der Kohlehydratgehalt 180—300 g pro Tag ausmachen solle, die Fettmenge 50 g pro Tag und das Eiweiss 15 % der ganzen Anzahl Kalorien. Bei Fieberkrankheiten lässt er Fett und Eiweiss aus der Kost weg.

STOLTE schätzt die Mortalität des Kinderdiabetes bei strenger Diät auf 29 %, bei kohlehydratreicher Kost auf 17 % und bei freier Kost auf 10 %. Ganz kürzlich veröffentlichte LICHTENSTEIN die ungemein guten Resultate, die in Schweden in den 10 Jahren von 1934—1943 bei der Behandlung des Kinderdiabetes mit freier Kost gemacht worden sind; die Mortalität (169 Fälle) stieg nur auf 4,7 %.

Seit Herbst 1934 sind sämtliche Kinder mit Diabetes in der Kinderklinik der Universität Helsingfors ohne die gewöhnlichen Diätvorschriften behandelt worden. Im Jahre 1936 veröffentlichte Rählä die Resultate der Nachuntersuchung der 44 Patienten, die bis zum 1.1.1936 auf diese Weise behandelt worden waren. Auch seine Erfahrungen über die neue Therapieform waren sehr positiv: Nicht einmal der sechste Teil der Kinder war unter der Observationszeit gestorben.

Da nunmehr über 10 Jahre vergangen sind, seit die freie Kost bei der Behandlung der Kinderdiabetes in unserer Klinik in Gebrauch genommen worden ist, dürfte es angebracht sein, auf Grund einer längeren Observationszeit und grösseren Materials zu untersuchen, welchen Einfluss die neue Behandlungsweise auf die Prognose gehabt hat. Nur LICHTENSTEINS oben erwähnte Publikation umfasst die Erfahrungen einer längeren Zeit mit »freier Kost».

Die Gesamtanzahl der Diabetespatienten, die in der 10-Jahresperiode von 1934—1943 in der Kinderklinik behandelt wurden, betrug 271, und davon lagen die meisten mehrere Male im Krankenhaus. Das Material, dass auch diejenigen Fälle enthält, die Räihä 1936 dargestellt hat, ist also für europäische Verhältnisse gross.

Um in Erfahrung zu bringen, welches Schicksal die Diabetes-

kinder später getroffen hat, habe ich die Journalen durchgesehen. Im Frühjahr 1945 wurden den Eltern der Kinder 253 Fragebogen zur Beantwortung übersandt; diejenigen, deren Kinder, 18 im ganzen, im Krankenhaus gestorben waren, erhielten das Formular nicht. Bis zum 1.10. 1945 waren 185 Antworten (73,1%) eingegangen, so dass das Ergebnis der Nachfrage also als gut betrachtet werden kann.

Nach meinen früheren Untersuchungen liess sich eine jährliche Zunahme der Anzahl neuer, in der Kinderklinik behandelter Diabetesfälle wahrnehmen. Die folgende Tabelle veranschaulicht die Anzahl der Fälle, die bei uns in den Jahren 1934—1943 behandelt worden sind:

Jahr	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	Zus.
Anzahl Fälle	32	30	18	23	39	28	28	20	22	31	271

Die Tabelle zeigt keine ständige Zunahme der Anzahl neuer Diabetiker.

Die Todesfälle.

Von den 185 in der Kinderklinik der Universität Helsingfors behandelten Kindern, über welche durch die Umfrage Angaben erhalten wurden, waren 69 gestorben, während 116 noch am Leben waren. In der Kinderklinik starben 18 Kinder. Die Anzahl der Fälle, über welche Angaben vorliegen, beträgt demnach 203. Von diesen Patienten waren 87 gestorben. Trotz der neuen Therapieform hat unser Land also immer noch sehr betrübliche Zahlen aufzuweisen. Die Mortalität ist grösser als in vielen Ländern vor der Periode, in welcher freigewählte Kost in Gebrauch genommen wurde.

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Die Todesursachen.

Bei den 18 Kindern, die in der Kinderklinik starben und die sämtliche aus Landgegenden stammten, war die Todesursache in 9 Fällen unkompliziertes Coma diabeticum, in 2 Fällen Hypoglykämie und in 7 Fällen interkurrente Krankheiten (Pneumonie, Sepsis, Nephritis, Lungentuberkulose). Von den 9 Fällen, die in unkompliziertem Koma gestorben waren, waren 7 nur 1—2 Tage im Krankenhaus behandelt worden; die Kinder befanden sich schon bei der Einlieferung in die Klinik in weit vorgeschrittenem Stadium von Intoxikation. Hier liegt die Annahme nahe, dass der vermutlich lange Weg zum nächsten Arzt und Krankenhaus in diesen Fällen sehr dazu beigetragen hat, dass die Kinder in so gut wie hoffnungslosem Zustand in der Kinderklinik eintrafen.

Nach den 69 Antworten der Eltern von Kindern zu beurteilen, die nach der Entlassung aus dem Krankenhaus gestorben waren, war die Todesursache in 46 Fällen Koma, in 5 Fällen Hypoglykämie. 14 Kinder starben an verschiedenen akuten Infektionskrankheiten. In 2 Fällen war die Todesursache Lungentuberkulose. Ein Kind ertrank und eines war im Anschluss an eine Blinddarmoperation gestorben.

In 3 von den »Hypoglykämiefällen» waren die Kinder während des letzten Krieges durch einen Luftangriff erschreckt worden und waren bald danach gestorben. Von den »Komafällen» verdienen folgende 4 besondere Erwähnung: In einem Fall war die Familie wegen des Winterkriegs in eine Gegend evakuiert worden, wo Insulin schwer zu beschaffen war, in einem Fall konnte die Apotheke infolge zeitweilig herrschenden Mangels an Insulin im vorigen Krieg dem Patienten die in Frage stehende Medizin nicht liefern, in einem Fall war der Patient nur dann mit Insulin behandelt worden, »wenn sich Zucker im Urin zeigte», und schliesslich musste in einem Fall mit der Insulinbehandlung aufgehört werden, weil der Patient wegen eines Tumors in der Cardiagegend keine Nahrung aufnehmen konnte.

Die Behandlung mit freier Kost scheint demnach keine Verschiebung in der Verteilung der verschiedenen Gruppen der Todesursachen, die ich früher aus der 10-Jahresperiode 1914—1933 veröffentlicht habe, hervorgerufen zu haben.

Patienten, die noch am Leben sind.

a) Physische Entwicklung.

In 57 Fällen wurde angegeben, dass der Allgemeinzustand ausgezeichnet, sehr gut oder gut war. In 49 Fällen war das Allgemeinbefinden relativ gut oder zufriedenstellend gewesen. In 2 Fällen war das Befinden variierend, 8 Patienten fühlten sich relativ schlecht oder schlecht. Zwei von den Letztgenannten, der eine 20- und der andere 12-jährig, leiden an weit fortgeschrittener Lungentuberkulose, in einem Fall war die Insulinbehandlung zeitweilig unterbrochen worden wegen ökonomischer Schwierigkeiten, 2 Kinder leiden an Epilepsie, 1 Patient hat seinen Herzfehler, Nierenleiden und Gelenkrheumatismuss und in einem ist die Zuckerkrankheit durch ein Nierenleiden und sirgendetwas im Herzens kompliziert. Ein 16 Jahre alter Knabe wird nunmehr mit Diät behandelt, welche u. a. in einer Einschränkung des Brotgenusses besteht.

Der Zeitpunkt für die Menarche dürfte bei den Mädchen als ein Kriterium der physischen Entwicklung angesehen werden können. Bei 22 über 15 Jahre alten weiblichen Diabetikern hatte die Menstruation mit 14 Jahren begonnen (3 Fälle), mit 15 Jahren (4 Fälle), mit 17 Jahren (3 Fälle), mit 18 Jahren (2 Fälle), mit 19 Jahren (1 Fall) und mit 20 Jahren (1 Fall). Von diesen war so gut wie bei allen die körperliche Entwicklung als gut oder normal bezeichnet worden. Bei 6 über 15 Jahre alten Mädchen hatte die Monatsblutung noch nicht begonnen mit 15 Jahren (1 Fall), mit 16 Jahren (1 Fall), mit 18 Jahren (1 Fall), mit 19 Jahren (3 Fälle) und mit 20 Jahren (1 Fall). Ihre physische Entwicklung war laut den Angaben schwach oder zurückgeblieben.

Bei 35 jungen Männern im Alter von 25—16 Jahren war die Geschlechtsreife in den meisten Fällen normal gewesen (Pubes, Stimmbruch). Nur in 2 Fälle war sie als »nicht ganz befriedigend» bezeichnet worden. Die körperliche Entwicklung war in 25 Fällen gut oder normal. Zehn junge Männer im gleichen Alter wiesen schwache oder zurückgebliebene physische Entwicklung auf.

Die Diagramme 1—4 veranschaulichen die Länge- und Gewichtsverhältnisse bei den Diabetikern im Alter von 3—20 Jahren. Zum Vergleich sind die von RUOTSALAINEN und TUNKELO angegebenen Tabellen über die durchschnittliche Länge und das durchschnittliche Gewicht bei 3—7 Jahre alten gesunden Kindern bezw. 7—20 Jahren alten Schülern benutzt worden, welche Tabellen in den Jahren 1922 und 1936 veröffentlicht worden sind. Leider waren keine numerischen Angaben aus den letzten Jahren zu finden, aber man kann annehmen, dass die Zahlen

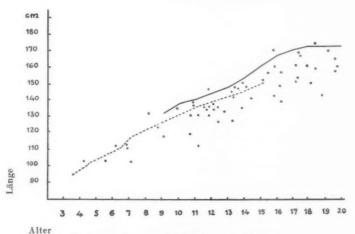


Diagramm 1: Länge bei Knaben mit Diabetes.

Durchschnittliche Länge bei Knaben im Alter von 3—7 Jahren (nach RUOTSA-AILNEN) und bei Volksschülern im Alter von 7—15 Jahren (nach TUNKELO)

Durchschnittliche Länge bei Schülern der Mittelschulen im Alter von

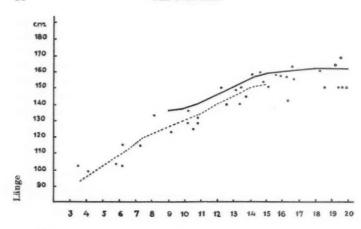
9—20 Jahren (nach TUNKELO)

für die durchschnittliche Länge und das durchschnittliche Gewicht gegenwärtig etwas grösser sind.

Aus Diagramm 1 geht hervor, dass die jungen männlichen Diabetiker meistens eine Länge haben, die bei gesunden Kindern im entsprechenden Alter gewöhnlich ist. Ein geringerer Teil von ihnen weist Werte für die Länge auf, die für kleiner als normal gelten können.



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Diagramm 2: Länge bei Mädchen mit Diabetes.

Durchschnittliche Länge bei Mädchen im Alter von 3—7 Jahren (nach Ruotsa-Lainen) und bei Volksschülerinnen im Alter von 7—15 Jahren (nach Tunkelo)
---- Durchschnittliche Länge bei Schülerinnen der Mittelschulen im Alter von
9—20 Jahren (nach Tunkelo)

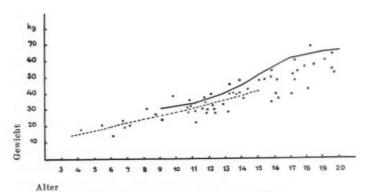


Diagramm 3: Gewicht bei Knaben mit Diabetes.

Durchschnittliches Gewicht bei Knaben im Alter von 3—7 Jahren (nach Ruotsalainen) und bei Volksschülern im Alter von 7—15 Jahren (nach Tunkelo) --- Durchschnittliches Gewicht bei Schülern dittelschulen im Alter von 9—20 Jahren (nach Tunkelo) ——

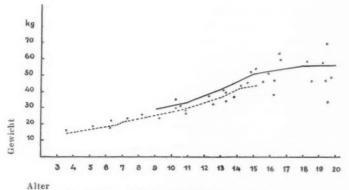


Diagramm 4: Gewicht bei Mädchen mit Diabetes.

Durchschnittliches Gewicht bei Mädchen im Alter von 3—7 Jahren (nach Ruotsalainen) und bei Volksschülerinnen im Alter von 7—15 Jahren (nach Tunkelo) ---- Durchschnittliches Gewicht bei Schülerinnen der Mittelschulen im Alter von 9—20 Jahren (nach Tunkelo) —

Diagramm 2 zeigt, dass die Länge der Mädchen und der jungen Diabetikerinnen fast ohne Ausnahme den normalen Wert erreicht. Nur in einigen vereinzelten Fällen ist die Länge zu gering.

Die Diagramme über das Gewicht zeigen ungefähr die gleichen Verhältnisse wie diejenigen über die Länge. In Diagramm 3 sieht man, dass ungefähr 10 Knaben und junge Männer ein geringeres Gewicht haben als für ihr Alter gewöhnlich ist, während die übrigen ein ziemlich normales Gewicht aufweisen. Aus Diagramm 4 geht hervor, dass die Mädchen und die jungen Diabetikerinnen fast ausnahmslos ein Gewicht haben, das die normalen Werte nicht unterschreitet. Nur in einigen wenigen Fällen wurde ein deutlich zu niedriger Wert festgestellt. Dagegen hat es den Anschein, dass ein höheres Gewicht als normal, besonders in den älteren Jahrgängen, nicht ganz ungewöhnlich ist. Von einer allgemeinen Neigung zur Korpulenz lässt sich auf Grund des vorliegenden Materials jedoch nicht sprechen.

Der Schulbesuch der Kinder verlief in fast allen Fällen normal und ohne Unterbrechung. Die allermeisten haben sich nach Ab-

schluss der Schule zu einem Beruf ausgebildet. Manche von den jungen Männern haben schwere körperliche Arbeit verrichtet, wovon Holzflössen und Landarbeit erwähnt seien. Einer von den Patienten dient als Heizer in einem Schiff. Infolge einer anderen Krankheit (Gelenkrheumatismus, Nierenleiden und Herzfehler nach Diphterie) sind die Patienten in einigen vereinzelten Fällen nicht imstande gewesen, einen Beruf auszuüben. Auch Sport und Freiluftleben ist von den allermeisten betrieben worden. Eines von den Mädchen hat dazu keine Zeit gehabt, weil sie so »schrecklich gern tanzt».

Bezüglich der jüngeren Kinder wurde angegeben, dass sie unbehindert mit ihren gesunden Altersgenossen spielen und lärmen.

Im Hinblick auf die physische Entwicklung bedeutet die Behandlung mit freier Kost einen entschiedenen therapeutischen Fortschritt. Aus meinen früheren Untersuchungen, die zur Diätperiode zählen, ging hervor, dass eine prozentuell bedeutend grössere Anzahl Patienten Zurückgebliebenheit in der körperlichen Entwicklung aufwies.

b) Psychische Entwicklung.

Schon früher sind alle Autoren der Ansicht gewesen, dass sich die Diabeteskinder psychisch in völlig gleicher Weise entwickeln wie die gesunden Kinder. Die Einführung der freien Kost hat keine grössere Veränderung in dieser Hinsicht mit sich gebracht.

Die Antworten auf unsere Rundfrage bestärken die Auffassung, dass die Diabeteskinder nicht nur auf gleichem intellektuellem Niveau stehen können wie andere Kinder, sondern diese oft sogar übertreffen. Nur in wenigen Fällen haben die zuckerkranken Kinder schlechte Schulzeugnisse erhalten. In vielen Fällen waren sie Klassenerste gewesen, recht häufig hatten sie gute oder sehr gute Zeugnisse aufzuweisen. Nur 8 Kinder hatten repitiert.

c) Hautsymptome, Augensymptome, Harnbeschwerden.

Trockene Haut, Pruritus, Pyodermie und andere Hautkrankheiten waren nur bei einer geringen Anzahl von Patienten vorgekommen: Trockene Haut war in 17 Fällen aufgetreten, Hautjucken in 12 Fällen, Eiterbildung in der Haut in 7 Fällen sowie Intertrigo und spröde Nägel in ein paar Fällen. Die meisten von den Kindern hatten derartige Symptome überhaupt nicht gehabt, und diejenigen, bei welchen sie vorkamen, hatten gewöhnlich mehrere von den Symptomen gleichzeitig gehabt.

Das Sehvermögen ist laut den Angaben mit Ausnahme von 2 Fällen bei allen gut gewesen. In 10 Fällen hatte sich das Sehvermögen im Verlauf der Krankheit mehr oder weniger verschlechtert; in einem davon hatte ein Nierenleiden noch dazu beigetragen. Nur 8 Patienten gebrauchten eine Brille; bei einem davon hatte die Brille das Sehvermögen nicht nennenswert verbessert.

In 25 Fällen waren die Patienten gezwungen gewesen, 2—4 mal in der Nacht zu urinieren, in 22 Fällen 0—1 mal. Bei den übrigen war nächtliches Harnlassen nicht vorgekommen.

d) Akute Infektionskrankheiten, Tuberkulose.

Wie bekannt ist der Krankheitsverlauf bei Diabetes von Kindern oft durch Infektionen verschiedener Art kompliziert. Kinder mit Zuckerkrankheit werden als in hohem Grad für akute Infektionskrankheiten empfänglich angesehen.

Von den 116 jetzt noch lebenden Patienten hatten, wenn man von leichten »Erkältungskrankheiten» absieht, 24 verschiedene akute Infektionskrankheiten durchgemacht, unter welchen folgende erwähnt seien: Gelbsucht (5 Fälle), Scharlach (1 Fall), Masern (5 Fälle), Diphterie (4 Fälle), Keuchhusten (2 Fälle), Windpocken (2 Fälle), Röteln (2 Fälle), Nephritis (4 Fälle), akute Polyarthritis (2 Fälle) und Mastoiditis (1 Fall).

Ausserdem hatten sich 2 Kinder wieder erholt, nachdem sie an Lungentuberkulose bezw. Rippenfellentzündung erkrankt waren.

Die Morbidität scheint nicht grösser zu sein als bei nichtzuckerkranken Kindern.

Insulin.

Alle 69 gestorbenen Patienten hatten zu hause Insulin benutzt. Die Behandlung war so gut wie allen Fällen regelmässig durchgeführt worden. In 2 Fällen hatten Schwierigkeiten bei der Beschaffung des Insulins, wie früher schon erwähnt worden ist, zum letalen Ausgang der Krankheit beigetragen. In 3 Fällen war die Insulintherapie wegen ökonomischer Schwierigkeiten unregelmässig gewesen. In 1 Fall war das Insulin nur dann angewandt worden, »wenn Zucker im Harn vorkam». Die Kommune hatte in 4 Fällen laut Angabe die Kosten für die Medizin bestritten.

Sämtliche 116 noch lebenden Patienten haben nach der Entlassung aus dem Krankenhaus Insulin benutzt. Mit 2 Ausnahmen war die Behandlung in allen Fällen ununterbrochen fortgesetzt worden; in 1 Fall hatte die Behandlung zeitweilig, in dem anderen ganz aufgehört, und zwar wegen ökonomischer Schwierigkeiten. Die absolute Mehrzahl der Patienten hatte, wenigstens am Anfang, Zink-Protamininsulin angewandt. In mehreren Fällen war man wegen Schwierigkeiten dieses Präparat zu beschaffen, während des Krieges und in der letzten Zeit gezwungen gewesen, zu "gewöhnlichem» Insulin überzugehen. In 22 Fällen hatte es Schwierigkeiten bereitet, überhaupt irgendein Insulinpräparat zu bekommen.

In 47 Fällen war der Insulinbedarf allmählich gestiegen, in 9 Fällen hatte die Insulindosis vermindert werden können, besonders im Sommer. In den übrigen Fällen nahmen die Patienten die gleiche Menge Insulin, wie bei der Entlassung aus dem Krankenhaus.

Die Kommune, eine Krankenkasse oder das Medizinalkollegium hatten für 11 Patienten entweder ganz oder teilweise die Kosten für das Insulin bestritten. In den übrigen Fällen hatten die Eltern oder die Patienten selbst die Medizin bezahlt.

Harnuntersuchung, Kontrolluntersuchung, Länge des Wegs bis zum Arzt oder Krankenhaus.

In 35 von den 69 Fällen, wo die Patienten nach der Entlassung aus dem Krankenhaus gestorben waren, war der Harn

zu hause regelmässig untersucht worden: Jeden Tag in 2 Fällen, einmal in der Woche in 5 Fällen, zweimal pro Monat in 5 Fällen, einmal pro Monat in 6 Fällen und ausserdem »oft», »mehrere Male», jeden zweiten Monat in 17 Fällen. In 8 Fällen war der Urin 1—3 mal pro Jahr oder »selten» untersucht worden. In 2 Fällen starben die Kinder einige Tage nach der Entlassung aus der Kinderklinik, nachdem sich ihr Zustand auf der Heimreise verschlechtert hatte.

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In 33 Fällen hatten die Patienten mehr oder minder regelmässig den Arzt zur Kontrolluntersuchung aufgesucht. In 6 Fällen war dies 1—2 mal pro Jahr oder »selten» geschehen. 22 Kinder waren nach der Entlassung aus dem Krankenhaus nicht mehr zum Arzt gebracht worden.

Die Länge des Wegs bis zum nächsten Arzt wurde in 46 Fällen angegeben, und sie betrug in 19 Fällen 0—5 km, in 9 Fällen 6—10 km, in 3 Fällen 11—15 km, in 7 Fällen 16—20 km, in 7 Fällen 21—30 km und in 1 Fall 100 km.

Der Weg bis zum nächsten Krankenhaus wurde in 39 Fällen mitgeteilt und war in 12 Fällen 0—5 km, in 6 Fällen 6—10 km, in 3 Fällen 11—15 km, in 8 Fällen 16—20 km, in 8 Fällen 21—30 km und in 1 Fall 45 km sowie in 1 Fall 100 km.

In 105 von den 116 Fällen, wo die Patienten noch am Leben waren, waren Angaben über die Harnuntersuchung gemacht worden. Diese war regelmässig in 49 Fällen vorgenommen worden: Jeden Tag in 3 Fällen, einmal pro Woche in 7 Fällen, zweimal pro Monat in 6 Fällen, einmal pro Monat in 19 Fällen sowie »oft», »mehrere Male», jeden zweiten Monat in 14 Fällen. In 39 Fällen war der Urin 1—3 mal pro Jahr oder »selten» untersucht worden. In 17 Fällen hatte nach der Entlassung aus dem Krankenhaus keine Harnuntersuchung stattgefunden.

In den 102 Fällen, über welche Angaben gemacht worden waren, hatte die Kontrolluntersuchung beim Arzt folgendermassen stattgefunden: »Regelmässig» und »oft» in 36 Fällen, 1—2 mal pro Jahr in 26 Fällen, »unregelmässig» und »selten» in 16 Fällen und überhaupt nicht in 24 Fällen.

Die Länge des Wegs bis zum nächsten Arzt war in 98 Fällen angegeben worden, und sie betrug in 48 Fällen 0-5 km, in 13

Fällen 6—10 km, in 13 Fällen 11—15 km, in 7 Fällen 16—20 km, in 10 Fällen 21—30 km und in 7 Fällen über 30 km, davon in 1 Fall 140 km und desgleichen in 1 Fall 230 km.

Der Weg bis zum nächsten Krankenhaus war in 36 Fällen 0—5 km, in 11 Fällen 6—10 km, in 12 Fällen 11—15 km, in 8 Fällen 16—20 km, in 10 Fällen 21—30 km und in 14 Fällen 45—230 km.

Alter beim Ausbruch der Krankheit, Todesalter, Duration, Todesjahr.

Das Alter beim Ausbruch der Krankheit, das anamnestisch in 253 Fällen festgestellt werden konnte, geht aus der untenstehenden Tabelle hervor:

Alter beim Ausbruch d. Krankheit	-1	-2	—3	-4	5	-6	-7	-8
Anzahl Fälle	5	18	13	30	13	15	17	26
Alter beim Ausbruch d. Krankheit	-9	-10	-11	-12	-13	-14	-15	Zus.
Anzahl Fälle	19	12	20	23	29	13	13	253

Die Tabelle weist 3 Höhepunkte auf mit einem Maximum für das 4., 8. und 13. Lebensjahr, was mit den Beobachtungen übereinstimmt, die bezüglich der 10-Jahresperiode 1914—1933 gemacht worden sind. In 5 Fällen hatte sich die Zuckerkrankheit während des ersten Lebensjahrs manifestiert.

Aus der folgenden Tabelle geht hervor, in welchem Alter die Patienten starben:

Alter beim Tode	-1	-2	-3	-4	-5	-6	— 7	-8	-9
Anzahl Fälle	1	2		7	4	6	2	6	7
Alter beim Tode	10	—11	-	12	13	-14	-	-15	-16
Anzahl Fälle	8	_	1		14	7		9	6

Alter beim Tode	-17	-18	-19	-20	21	-22	-23	Zus.
Anzahl Fälle	2	1	_	2	1	_	1	87

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Die Sterblichkeit war also, wie aus dem Obigen hervorgeht, unter den jüngsten Kindern nicht grösser als unter den älteren.

Über die Duration der Krankheit, die sich in 84 von den 87 gestorbenen Fällen ermitteln liess, wurde folgende Tabelle aufgestellt:

Duration d. Krankheit in Jahren	—1	-2	-3	-4	5	6	-7	8
Anzahl Fälle	26	14	11	11	10	3	5	_
Duration d. Krankheit in Jahren	9	10	—11	-12	13	-14	15	Zus.
Anzahl Fälle	1	1	_	-	1		1	84

Während des ersten Jahrs der Krankheit waren 26 Kinder gestorben (31 %), innerhalb der drei ersten Krankheitsjahre 51 Kinder (60,7 %); die durchschnittliche Duration betrug 3 Jahre und 4 Monate, was eine Verlängerung von nahezu 2 Jahren ausmacht im Vergleich zu den Erfahrungen, die aus der Periode vor der Einführung der freien Kost gemacht worden waren.

Um zu ermitteln, in welchem Kalenderjahr die meisten Todesfälle eingetroffen waren unter denjenigen Patienten, welche nach der Entlassung aus der Kinderklinik gestorben waren, wurde folgende Tabelle zusammengestellt:

Jahreszahl	1934	1935	1936		1937	1938	1939
Anzahl Todesfälle	1	5	1		1	1	6
Jahreszahl	1940	1941	1942	1943	1944	1945	Zus.
Anzahl Todesfälle	13	12	5	12	7	5	69

Wenn man die erste Hälfte von der Periode, die die Tabelle umfasst, d.h. die Vorkriegsjahre 1934—39 mit der anderen Hälfte, d. h. die Kriegsjahre 1940—45 vergleicht, so stellt man fest, dass die meisten Todesfälle (78,3 %) in den Kriegsjahren eingetroffen waren.

Diskussion.

Im allgemeinen weist der Kinderdiabetes Tendenz zur Verschlimmerung auf. Tillgren, Söderling, Landabure, Boyd u. a. m. sind der Ansicht, dass der Insulinbedarf bei Kindern mit regulärem Diabetes, nach allen Beobachtungen zu beurteilen, von Jahr zu Jahr zunimmt. Auch in meinen Fällen konnte meistens eine Progression der Krankheit festgestellt werden. Die Behandlung ohne Diät scheint keine Veränderung im Hinblick auf den steigenden Insulinbedarf mit sich gebracht zu haben. Fälle von Heilung kamen nicht vor.

Die Gefahr für das Auftreten vom Hypoglykämie scheint offensichtlich abgenommen zu haben; ob dies der freigewählten Kost oder der Einführung von Zink-Protamininsulin in der Therapie zuzuschreiben ist, lässt sich schwer beurteilen. Es ist wahrscheinlich, dass beide dazu beigetragen haben. Eine kohlehydratreichere Nahrung hält den Zuckergehalt des Bluts und des Urins auf höherem Niveau, während das Zink-Protamin eine gleichmässigere, protrahierte Insulinwirkung hervorruft.

In 3 von den Fällen, wo der Tod durch Hypoglykämie verursacht worden war, waren die Kinder durch ein Luftbombardement erschreckt worden; es ist eine wohlbekannte Tatsache, dass psychische Insulte für die Diabeteskinder grosse Gefahr enthalten. In den weiteren 2 Fällen waren die Kinder einige Tage nach der Entlassung aus der Kinderklinik gestorben, nachdem sich ihr Zustand auf der Heimreise verschlechtert hatte. Auch in diesen Fällen kann man sich denken, dass der psychische Stimmungsumschlag, der bei den Kindern eintrifft bei dem Gedanken, nun nach Hause kommen zu dürfen, zu dem deletären Ausgang beitragen konnte.

In 10 von den Fällen, wo die Kinder in der Kinderklinik starben, handelte es sich um die akute Form des Diabetes, die bei Erwachsenen selten vorkommt. Die Krankheit war kurz vor der Aufnahme ins Krankenhaus diagnostiziert worden, und die Kinder befanden sich in tiefem reaktionslosem Koma.

Wie zu Beginn dieser Arbeit schon erwähnt worden ist, stammten die allermeisten Kinder aus Landgegenden. Nur 17 wohnten in Helsingfors, und von diesen waren in 11 Fällen Angaben erhalten worden. Nur 1 Kind war gestorben. Die Prognose für die Kinder aus Helsingfors gestaltet sich sicherlich viel günstiger als für Kinder, die auf dem Lande wohnen. Um diese Frage auf Grund eines grösseren Materials zu beleuchten, habe ich die Absicht, in Kürze die Resultate von Nachuntersuchungen bei denjenigen Patienten zu veröffentlichen, welche in der 10-Jahresperiode 1934—43 in der Kinderabteilung des Maria-Krankenhauses in Helsingfors wegen Diabetes mellitus behandelt worden sind.

Weshalb bekommen wir mit unserer Behandlung nicht ebenso gute Resultate wie in anderen Ländern? Worauf beruht es, dass die Mortalität bei uns zehnmal grösser ist als z.B. in unserem westlichen Nachbarland, obwohl die Behandlungsprinzipien in beiden Ländern genau die gleichen sind?

In Finnland spielen ökonomische und soziale Umstände eine grosse Rolle bei der Behandlung. Der Lebensstandard im allgemeinen ist bei uns ohne Zweifel bedeutend niedriger als in Schweden. In viel mehr Fällen, als direkt durch die Rundfrage zum Vorschein kam, hat die Armut der Eltern sicherlich der Beschaffung rationeller und vollwertiger Kost für die Kinder Hindernisse in den Weg gestellt, wodurch die allgemeine Widerstandskraft der Patienten vermindert wurde. Die Nahrung der armen Bevölkerung ist in unserem Lande immer einförmig gewesen und besteht hauptsächlich aus Kohlehydraten; in den Kriegsjahren wurde deren Anteil an der Nahrung immer grösser. Ökonomische Schwierigkeiten haben auch dazu beigetragen, dass die Kontrolluntersuchung durch den Arzt nicht so oft vorgenommen werden konnte, wie es wünschenswert gewesen wäre. Die Überwachung des Befindens der Patienten ist in gewissen Fällen dadurch erschwert worden, dass der Weg bis zum nächsten Arzt und Krankenhaus lang gewesen ist. Dass es im Hinblick auf eine erfolgreiche Behandlung der Kinderdiabetes ein bedeutender Vorteil ist in einer Stadt zu wohnen, dürfte ausserhalb jeden Zweifels liegen. Bei kritischen Gelegenheiten kann der Arzt schnell herbeigerufen werden, Spezialistenbehandlung steht zur Verfügung, der Weg zum Krankenhaus ist kurz, der Transport bedeutend billiger, die Beschaffung von Insulin ist leichter usw.

Es liegt auf der Hand, dass die Kriegsjahre zum grossen Teil zu der schlechten Prognose beigetragen haben. Wie schon oben erwähnt worden ist, trafen 78,3 % von den Todesfällen, wo die Patienten, von welchen Angaben erhalten worden waren, nach der Entlassung aus dem Krankenhaus starben, in den Kriegsjahren 1940—45 ein. Unsere verschlechterte Nahrungslage, der Mangel an Kleidungsstücken, die Schwierigkeit der Beschaffung von Insulin und besonders Zink-Protamininsulin, die stark verschlechterten Verkehrsmittel, die Evakuierung grosser Bevölkerungsgruppen, der Mangel an Ärzten (wegen Einberufungen zum Militärdienst) usw. haben sicherlich viel die hohe Mortalität begünstigt.

Was kann nun getan werden, um die Prognose bei Kinderdiabetes in Finnland zu verbessern? Es wäre vielleicht Grund
vorhanden, in jeder Gemeinde von den Gesundheitsschwestern
geleitete Kontrollstationen einzurichten. Die Patienten sollten
gezwungen werden, sich mit regelmässigen Zwischenzeiten dort
zur Untersuchung einzustellen. Ausserdem sollte von den Gesundheitsschwestern Hausbesuche gemacht werden. Bei Bedarf
sollten die Letzteren den Arzt zu Rate ziehen.

Die Kommunen sollten in höherem Grad als bisher den Minderbemittelten für die Beschatfung von Insulin und die Ermöglichung regelmässiger ärztlicher Behandlung Unterstützung bezahlen.

Die Kinder sollten während der Heimreise vom Krankenhaus genau überwacht werden.

Der Zustand der Diabeteskinder scheint besonders kritisch in den Präpubertäts- und den Pubertätsjahren zu sein, weshalb in dieser Periode besondere Aufmerksamkeit vonnöten ist.

In meinem Material war die Mortalität am grössten in den 3 ersten Krankheitsjahren; der Gesundheitszustand der Kinder sollte in diesen Jahren also äusserst sorgfältig überwacht werden. Eine rationelle Diabetesbehandlung im Kindesalter ist für das Gemeinwesen von grosser Bedeutung. Den Diabeteskindern fehlt es durchaus nicht Voraussetzungen, sich zu tauglichen und voll arbeitsfähigen Volksgenossen zu entwickeln.

Schlussfolgerungen.

Nach der Einführung der freien Kost in der Behandlung des Diabetes mellitus bei Kindern in Finnland scheint die Mortalität gesunken zu sein. Die immer noch erstaunlich grosse Sterblichkeit beruht meines Erachtens nicht auf eine Schwäche der Behandlungsprinzipien selbst, sondern auf den Schwierigkeiten, welche in Folge des Krieges in unserem Lande die Kontrolle der rationellen Therapie, die die Behandlung des Diabetes voraussetzt, unmöglich machten. Nichts spricht indessen gegen die Annahme, dass, nachdem unser Land sich von den Anstrengungen des Kriegs erholt hat, eine freigewählte Kost für die Kinderdiabetiker die Verbesserung der Prognose mit sich bringen könnte, die man früher auf vielen Seiten zu konstatieren konnte.

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Zur Frage der paroxysmalen Tachykardie und des Herzflatterns in den ersten Lebenswochen.

Von

ERIK FRISELL.

Unregelmässigkeiten der Herztätigkeit vom Typus der paroxysmalen Tachykardie oder des Herzflatterns sind in den ersten Lebenswochen etwas Seltenes. In den letzten zwanzig Jahren sind verschiedentlich Einzelfälle beschrieben worden, deren Gesamtzahl jetzt 15 übersteigt. Diese Erkrankungen sind aber keineswegs bedeutungslos, da die Gefahr des Versagens der Herzkraft und der Tod drohen, wenn die Kinder unbehandelt bleiben. Auf der anderen Seite hat eine lege artis durchgeführte Digitalisbehandlung ausgezeichnete Ergebnisse geliefert.

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Auch während des übrigen Teils des ersten Lebensjahres ist die paroxysmale Tachykardie ziemlich selten, immerhin aber wahrscheinlich häufiger, als es dem Schrifttum nach den Anschein hat, indem viele Fälle vermutlich nicht diagnostiziert werden. Es besteht kein grundsätzlicher Unterschied zwischen den in den ersten Lebenswochen und den später einsetzenden Erkrankungsfällen. Allerdings kristallisiert sich das klinische Bild im allgemeinen schärfer heraus, wenn der Säugling etliche Wochen oder Monate älter geworden ist, und aus diesem Grunde wird die Diagnose dann leichter gestellt. Von Herzflattern dagegen sind, wie wir unten noch sehen werden, keine Fälle beschrieben worden, bei denen die Erkrankung nach Ablauf der beiden ersten Lebenswochen aufgetreten wäre.¹ Diese Zeitspanne ist

¹ Herzflattern in der späteren Kindheit in Verbindung mit Diphtherie und anderen schwereren Infektionen ist u. a. von Neubauer beschrieben worden.

bei der vorliegenden Arbeit u. a. deshalb als Grenze genommen worden, um einen Vergleich zwischen den beiden Frequenzstörungen zu ermöglichen.

Nach der gebräuchlichen Bezeichnungsweise versteht man unter paroxysmaler Tachykardie bei Erwachsenen einen Zustand mit einer Herzfrequenz von gewöhnlich 150—200 Schlägen pro Minute; die Auslösung erfolgt von einem ektopischen Herd in der Vorhofswand, im Atrioventrikularknoten oder, in seltenen Fällen, in der Kammerwand. Es handelt sich um eine Serie von verfrühten Systolen, bei denen die Kammerwand nachträglich auf jede Vorhofkontraktion reagiert. Bei Säuglingen kann die Herzfrequenz in derartigen Fällen 250—300 Schläge pro Minute erreichen.

Das Vorhofsflattern, die einzige Form des Herzflatterns, die in praxi berücksichtigt werden muss, zeichnet sich durch eine rasche, regelmässige und koordinierte Vorhoftätigkeit aus, wobei die Schlagfolge eine so hohe ist, dass die Kammern nicht imstande sind, auf jeden Vorhofimpuls zu reagieren. Dabei kommt es zum partiellen oder kompletten Herzblock. Die Impulse gehen nicht länger vom Keith-Flackschen Knoten aus, sondern von irgendeiner anderen Stelle der Vorhofswand. Der diesbezügliche Mechanismus ist nach Lewis der, dass die Reize über die Vorhofmuskulatur in zirkulären Wellen das ganze Herz umlaufen, und zwar in so dichter Aufeinanderfolge, dass sich in jedem Augenblick irgendeine Muskelgruppe im Stadium der Kontraktion befindet. Gewöhnlich handelt es sich um einen regelmässigen Rhythmus, aber die Zahl der auf einen Kammerschlag entfallenden Vorhofschläge kann bei ein und demselben Individuum von einem Zeitpunkt zum anderen wechseln.

Bei Neugeborenen legt das klinische Bild den Verdacht auf eine dieser Störungen weniger nahe als bei älteren Kindern oder bei Erwachsenen. Schon die normale Pulsfrequenz liegt bei jenen zwischen 110 und 140 und kann bei Gelegenheit von Unruhe oder Erkrankung auf 180 und darüber hinaus steigen, ohne dass es sich um etwas anderes als den gewöhnlichen sinuaurikulären Rhythmus handelt. Der Puls ist in diesen Fällen schwer zu beurteilen, und die genaue Zählung der Herzschläge mittels des

Stethoskops wird wohl manchmal unterlassen. Anzeichen von Herzinsuffizienz können sich entweder spät bzw. überhaupt nicht einstellen, oder auch atypisch sein, z.B. Trägheit beim Saugen, Erbrechen, Verweigerung der Nahrung od. dgl. Volle Klarheit bringt in der Regel erst die Elektrokardiographie. Eine dauernde Schlagfolge von 200 und mehr muss als pathologisch gelten.

Über die Ursache der Anfälle wissen wir sehr wenig, und in der grossen Mehrzahl der Fälle hat sich weder ein auslösendes Moment noch ein organischer Herzfehler als Unterlage der Störungen nachweisen lassen. Bei 3 von 37 dem Schrifttum entnommenen Fällen von paroxysmaler Tachykardie während des ganzen ersten Lebensjahres fand Christensen ein sicheres kongenitales Vitium cordis (diese 3 Kinder kamen ad exitum), und ferner bestand bei 4 weiteren Fällen der Verdacht auf Herzfehler. Bei einem 10 Monate alten Kinde wurde als Ursache der Tachykardie ein Rhabdomyosarkom im Reizleitungssystem nachgewiesen, bei einem anderen eine idiopathische Herzhypertrophie, aber der tödliche Ausgang scheint bei keinem dieser beiden Fälle durch die Tachykardie verursacht gewesen zu sein.

Untersuchungen der letzten Jahre haben gelehrt, dass die paroxysmale Tachykardie in 5—10 % der Fälle, bei sowohl Erwachsenen wie Kindern, mit dem sog. W. P. W.-Syndrom oder der »pre-excitation» im Elektrokardiogramm einhergeht (Öhnell und Lind). Es soll sich hierbei um einen Reflux der Impulswelle durch das Kentsche Bündel von der Kammer zum Vorhof handeln; im letzteren wird eine erneute Vorhofkontraktion ausgelöst, bevor der nächste Impuls vom Keith-Flackschen Knoten ausgegangen ist. Das früheste Alter, in dem Präexcitation festgestellt wurde, ist das von 3 Wochen; Nádrai hat einen einschlägigen Fall ohne, Mannheimer einen solchen mit paroxysmaler Tachykardie beschrieben.

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Bei denjenigen Fällen von paroxysmaler Tachykardie und Herzflattern während der ersten Lebenswochen, die in Tabelle 1 aufgeführt sind, hat allem Anschein nach, soweit die Elektrokardiogramme der Beurteilung zugänglich waren, nirgends Präexcitation vorgelegen.

Nach einer der zur Erklärung der paroxysmalen Tachykardie

aufgestellten Theorien sollen einzelne oder multiple Entzündungsherde im Myokard den Ausgangspunkt von Reizen bilden können, die Unregelmässigkeiten der Herzaktion zur Folge haben. Ein Herd beispielsweise in der Vorhofwand soll durch den bei der Kammerkontraktion entstehenden mechanischen Reiz dazu gebracht werden, einen nervösen Impuls auszusenden, der eine verfrühte, sich in den sinuaurikulären Rhythmus interpolierende Herzkontraktion bewirkt. Diese Theorie illustriert ein von Piotti 1945 eingehend beschriebener Fall, der eines 11 Monate alten Kindes mit durch Behandlung nicht zu beeinflussender paroxysmaler Tachykardie, das nach fast einjähriger Krankheitsdauer dem Herzleiden zum Opfer fiel. Die Obduktion ergab eine mächtige Hypertrophie der linken Herzhälfte und eine interstitielle Myokarditis im rechten Vorhof einschliesslich des Gebiets zwischen Aschoff-Tawaraschem Knoten und Mündung des Sinus caroticus. Sonst war das Myokard unverändert.

In den zahlreichen Fällen, wo keinerlei organische Herzveränderungen zu finden sind, muss man nach Christensen annehmen, dass die Frequenzstörungen durch ein Versagen der zentralen oder autonomen Steuerung des Herzens zustande kommt. Es ist daher keineswegs verwunderlich, dass die Anfälle oft kurz nach der Geburt einsetzen, an einem Zeitpunkt, an dem auch andere Steuerungsmechanismen, wie Wärme- und Blutzuckerregulierung, noch unvollkommen sind.

Die Frage des Wesens dieser Erkrankungen bei Neugeborenen sowie ihrer Beziehungen zueinander hat den Gegenstand von Erörterungen gebildet. Man hat paroxysmale Tachykardie für sich und Flattern für sich beschrieben, indem man damit zum Ausdruck brachte, dass man auf dem Standpunkt stand, es handle sich um verschiedene Krankheitszustände. Andere Autoren haben unter der Überschrift paroxysmale Tachykardie auch Fälle von Flattern besprochen, ohne darauf einzugehen, ob ihrer Ansicht nach irgendein Unterschied bestände. Hubbard macht darauf aufmerksam, dass es in vielen Fällen mit so hoher Herzfrequenz wie der, um welche es sich hier handelt, überaus schwierig ist, das Elektrokardiogramm zu deuten; bei der Feststellung, ob eine paroxysmale Tachykardie von Vorhofs- oder A-V-Ursprung

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³⁻⁴⁶⁸⁸⁵ Acta pædiatrica. Vol. XXXIV

vorliegt, oder ob es sich um Vorhofflattern mit Blockierung 1: 1 handelt, gehen die Meinungen oft auseinander. Ist eine deutliche P-Zacke vorhanden, so wird häufig eine entscheidende Diagnose ermöglicht. Erst bei Blockierung höherer Grade wird das Elektrokardiogramm leichter deutbar.

Wenn man, wie in Tabelle 1, sämtliche Fälle des Schrifttums von paroxysmaler Tachykardie und Flattern bei Neugeborenen nach dem Herzrhythmus laut Ekg zu einer steigenden Reihe ordnet, dann findet man im grossen und ganzen, dass zuerst alle Fälle mit paroxysmaler Tachykardie kommen, dann die Fälle mit Flattern. Ausserdem wurde der einzige Fall von Flimmern hinzugefügt, der im Schrifttum zu finden war. Mit Ausnahme von Werleys Fall, bei dem die Herzfrequenz nicht elektrokardiographisch festgestellt worden war, und Puglisis Fall mit einer Herzfrequenz von 345 - beide endeten tödlich -, liegt die Herzfrequenz bei den Tachykardiefällen unter und bei den Flatterfällen über 300 pro Minute. Der Übergang ist ein fliessender. Dies könnte darauf hindeuten, dass der Unterschied zwischen den Erscheinungen eher ein Grad- als ein Artunterschied ist. Die grosse Anpassungsfähigkeit des Säuglingsherzens hat zur Folge, dass die Kammern dem Tempo der Vorhöfe bis zu einer Schlagfolge von etwa 300 zu folgen vermögen, aber nicht weiter: die Kammermuskulatur befindet sich noch im Refraktärzustand, wenn der nächste Impuls vom Vorhof anlangt, und es kommt zur Blockierung. Bis zu welcher Höhe in der Reihe es sich um regelrechte Vorhofkontraktionen handelt, von einem ektopischen Herd ausgelöst, und wo die zirkuläre Reizwellenbewegung in der Vorhofmuskulatur nach Lewis beginnt, das lässt sich wohl kaum ermitteln. Dressler u. a. nehmen an, dass es sich bei allen diesen anfallsweise auftretenden Tachykardien bei Kindern um ein Vorhofflattern mit »Vollrhythmus» handelt.

Aus der tabellarischen Zusammenstellung wird ferner ersichtlich, dass bei mehreren der Fälle, wo das Elektrokardiogramm später Blockierung ergab, Unregelmässigkeiten der Herztätigkeit schon während des intrauterinen Lebens hatten konstatiert werden können. An diese schliesst sich eng ein Fall an, der von Tollas als »intrauterin festgestellte paroxysmale Tachykardie»

Tabelle 1.

Herzrhythmus Digitalis-

Bemerkungen

Resultai

behandlung

lant Ekg

Jahr Alter beim Einsetzen

Autor

-	4	
9	2	
-	Ħ.	
9	5	
7	2	

Alter beim Herzrhythmus Digitalis- Einsetzen laut Ekg behandlung Resultat Bemerkungen	Paroxysmale Tachykardie.	13 Tage 220 ja Genesung	beim Partus 225 ja Genesung	7 Tage 240 ja 0 Nach 4 Anfällen spontane Gene-	7 Tage 250-300 ja Genesung	264	10 Tage 270 ja Genesung Während der Digitalisbehand- lung vorübergeh. Vorhofflimmern 5-600·70	14 Tuge 300 nein Generung	300 ja	307 ¹ nein I	10 Tage 345 nein Exitus Reagierte nicht auf Chininbe- handlung	Plattern,	8 Tage 300:170 nein	beim Partus? 400:200 ja normaler Zustand schlecht seit Geburt. Rhythmus Diagnose u. Behandl. im Alter v. 3 Mon. Exitus 6 Mon. Nicht obduziert	vor d. Partus 420:210 nein Genesung Am 10. Tage normaler Rhythmus	vor d. Partus 440:220 ja Genesung	Vor d. Partus 464: 232 ja Genesung	ja zeitweise	100—250 normaler nose, Dyspnoe, Erbrechen usw. Rhythmus Diagnose im Alter v. 4 Mon. Rezidiv trotz Digitalis	Flimmern.	vor d. Partus 500-750 ja Genesung Bei d. Geburt wurde schneller u.
Jahr Alter b		1941 13 T	1942 beim P	1930 7 Ta	1937 7 Ta	1942 8 Ta	1941 10 T	1933 14 T	1945 4 Ta	1925 4 Ta	T 01 0E61		1932 8 Ta	1940 beim P.	1931 vor d. I	945 vor d. I	1934 vor d. I	1926 beim P:			
Autor		HUBBARD 1	TARNOWER II. LATTIN 1	Doxlades	TARAN U. JENNINGS 1	TARNOWER U. LATTIN 1	HUBBARD 1	DUKEN 1	Howard 1	Werley 1	PUGLISI		HECHT 1	MANNHEIMER 1	CARR U. MCCLURE 1	FRISELL 1	SHERMAN U. SCHLESS 1				GOLDBLOOM u. SEGALL 1938

1 Mit Polygramm bestimmt

beschrieben worden ist, bei dem aber die Krankengeschichte als Ganzes sich mit der jener Fälle deckt, die oben als Flattern klassifiziert worden sind. Da keine elektrokardiographische Untersuchung vorgenommen worden war, lässt sich die Diagnose nicht näher präzisieren.

Das Erscheinungsbild ist bei diesen Frühfällen von Herzfrequenzstörung nicht einheitlich, und Anzeichen von Herzinkompensation sind gewöhnlich weder so ausgesprochen noch so regelmässig vorkommend, wie beim Einsetzen oder Rezidivieren nach Ablauf der ersten Lebenswochen. Ein Beispiel hierfür ist der Fall von Doxiades, bei dem in Zwischenräumen von einigen Wochen vier Tachykardieattacken auftraten. Der erste Anfall im Alter von 7 Tagen hielt 9 Tage an und wurde nur von unerheblichen Inkompensationssymptomen begleitet. Bei den folgenden Anfällen mit einer Dauer von 10, bzw. 7 Tagen und 24 Stunden war das Kind dagegen wesentlich mehr mitgenommen, und die Inkompensationserscheinungen waren schwerer.

In der Hubbardschen Aufstellung von Tachykardiefällen bei älteren Säuglingen kehren Erscheinungen von Herzinkompensation mit beträchtlich grösserer Regelmässigkeit wieder, als es aus den Berichten über dieselbe Herzstörung bei Neugeborenen hervorgeht.

Diejenigen Symptome, welchen man immer wieder begegnet, wenn man die Angaben im Schrifttum sammelt, sind, neben der beschleunigten Herztätigkeit, gesteigerte Atmungsfrequenz bis zu 60—80 Atemzüge pro Minute, leichtere Formen von Zyanose und eine Lebervergrösserung bis um einige Querfinger. Ferner hat man in mehreren Fällen Stauungsgeräusche über den Lungen gehört oder im Röntgenbilde der letzteren eine Stauungszeichnung gefunden, ausserdem leichte Herzverbreiterung; überdies wollten die Kinder nicht trinken und hatten Erbrechen. In einer geringen Anzahl von Fällen sind Temperatursteigerung und Leukozytose (12 000—14 000 weisse Blk.) verzeichnet, in der überwiegenden Mehrzahl der Fälle aber fehlen diesbezügliche Angaben. Der Allgemeinzustand wechselt zwischen zeitweiliger starker Beeinträchtigung und völligem Wohlbefinden. Zusammenfassend sei hinzugefügt, dass die Angaben über viele der veröffentlichten

Fälle knapp und lückenhaft sind; es ist infolgedessen schwer, ein klares Bild des Sachverhalts zu entwerfen.

Man hat eine Reihe verschiedener Heilmittel erfolglos versucht: Morphin, Chinin, Chinidin, Physostigmin, Pilokarpin; ausserdem Brom, Chloralhydrat, Phenobarbital und allgemeine Sedativa. Daneben hat man eine Vagusreizung zu erzielen gesucht, z. B. durch Druck auf den Augapfel oder auf den Sinus caroticus, doch ohne Erfolg.

Auf der anderen Seite hat sich herausgestellt, dass Digitalis eine sehr günstige Wirkung hat, und es hat dies lange als das einzige Mittel gegolten, dessen Gebrauch bei diesen Fällen von beschleunigter Herztätigkeit begründet sei. In letzter Zeit hat man auch mit einem gewissen Erfolg Versuche mit den vagusreizenden Präparaten Neostigmin und Azetylcholin angestellt, unter Umständen in Kombination mit Digitalis. Was Digitalis selbst anlangt, so sind es dessen allgemein bekannte pharmakologische Eigenschaften, welche die theoretische Unterlage der Behandlung bilden. Digitalis verlangsamt die Reizleitung, verlängert den Refraktärzustand und setzt die Reizbarkeit des Herzmuskels herab; all das zielt darauf ab, die Anstrengung des Herzens einzuschränken. Ausserdem steigert Digitalis den Muskeltonus und hebt die kontraktile Kraft.

Dass aber immerhin eine gewisse Vorsicht mit diesem Mittel geboten ist, lehrt u. a. Taran und Jennings Fall von paroxysmaler Tachykardie beim Neugeborenen mit Ausgang vom Atrioventrikularknoten: Nach 0,2 g Digitalis intramuskulär sank die Herzfrequenz im Laufe von 50 Minuten von 250 auf 150. Ein Rückfall 9 Tage später wurde mit 0,1 g Digitalis intramuskulär behandelt, wobei die Herzfrequenz nach 1 Stunde plötzlich von 272 auf 143 Schläge pro Minute fiel. Gleich danach traten zwei kurze Attacken von Ventrikelflimmern ein, die im Ekg schön registriert wurden. Nach 2 weiteren Stunden herrschten wieder ganz normale Verhältnisse, und ein erneuter Rückfall wurde nie beobachtet.

Auch bei dem einen Fall von Hubbard bemerkt man Anzeichen einer Überdosierung. Es handelte sich um ein ausgetragenes Kind, das 0,1 g Digifolin intramuskulär bekam und nach Wiederholung der Dosis intramuskulär binnen 24 Stunden Anzeichen von unregelmässiger Herztätigkeit mit Vorhofflattern aufwies. Ziemlich bald traten aber wieder normale Verhältnisse ein.

Howard gab einem Kinde von 4 500 g in extremer Herzinsuffizienz 2 ml Digalen intramuskulär und konstatierte unmittelbar darauf einen vollständigen Herzblock mit einer Herzfrequenz von 60 Schlägen pro Minute. Angaben über den weiteren Verlauf fehlen.

Dosierung. Hubbard berechnet nach dem Körpergewicht die Dosis für volle Digitalisierung und empfiehlt auf Grundlage von 9 eigenen Fällen während des ganzen Säuglingsalters eine Anfangsdosis von 0,05—0,1 g intramuskulär für einen Neugeborenen von 3 500 g und eine gegebenenfalls wiederholte Dosis von 0,05 g. Normaler Rhythmus trat bei seinen Fällen nach 1—2 Tagen ein.

Howard empfiehlt die Hälfte der berechneten Dosis bei der ersten Injektion und dann, falls nötig, ein Viertel nach 4 Stunden. Bei seinem eigenen Fall wurde am 5. Lebenstage 0,1 bzw. 0,05 g Digalen mit 6 Stunden Zwischenraum gegeben. Dauernder normaler Herzrhythmus trat 9 Stunden nach der ersten Injektion ein.

Wie wir soeben gesehen haben, hat man im allgemeinen wenige, aber grosse Dosen gegeben. Es war bald der normale Rhythmus hergestellt, aber auf der anderen Seite sind Anzeichen von Überdosierung nicht ausgeblieben. Abgesehen von solchen Fällen, wo die Erhaltung des Lebens gebieterisch eine unmittelbare Abhilfe der Frequenzstörung fordert, sollte man vorsichtiger sein und Digitalis in kleineren Dosen zuführen, die dafür häufiger und längere Zeit hindurch gegeben werden. Von dieser Darreichungsweise ist bei dem Fall Gebrauch gemacht worden, über welchen Verf. unten berichten wird.

Geht man von diesem Fall aus, dann liegt folgender Gedankengang nahe: Auch wenn eine sekundär zur Frequenzstörung entstandene akute Herzinkompensation zur raschen Behebung der Frequenzstörung drängt, dürften sich durch eine niedrigere Dosierung mit geringerer Gefahr toxischer Nebenwirkungen dieselben guten Erfolge erzielen lassen, wie bei den Fällen im Schrifttum mit Anfangsdosen bis zu 0,2 g Digitalis, unter Umständen gefolgt von einer weiteren, halb so grossen Dosis.

Christensen u. a. haben entsprechend dem bei Erwachsenen seit langem erprobten Verfahren eine Kombination von Digitalis und einem vagusreizenden Präparat, Azetylcholin oder Neostigmin, vorgeschlagen, und zwar in Dosen, die bei jedem Mittel für sich therapeutisch wirkungslos sind. Durch Digitalis wird zuerst die Herzmuskulatur für das nachfolgende vagusreizende Präparat sensibilisiert, welches dann mit gutem Resultat in so kleiner Dosis gegeben werden kann, dass toxische Nebenwirkungen überhaupt nicht zu befürchten sind.

Das Ergebnis der Behandlung dieser Herzfrequenzstörungen bei Säuglingen ist allerdings stets schwer zu beurteilen, und zwar infolge der Neigung zu spontanen Remissionen. Was die Neugeborenen betrifft, so wird aus Tabelle ersichtlich, dass in etlichen Fällen ohne Behandlung Genesung erfolgte, und bei dem Fall von Doxiades hatte Digitalis keinen Einfluss auf die Tachykardieanfälle, die aber schliesslich von selbst aufhörten. Auf der anderen Seite verliefen zwei der unbehandelten Fälle tödlich, ohne andere nachweisbare Ursache als die paroxysmale Tachykardie.

Fallbeschreibung.

B. E. N., Knabe, geb. 4.6. 1944. Eltern gesund, im Alter zwischen 20 und 30 Jahre, nicht miteinander verwandt. Einziges Kind. In bezug auf erbliche Belastung sei erwähnt, dass der Vater im Alter von 9—10 Jahren während einiger Zeit wegen starken Herzklopfens bei Anstrengungen vom Schulturnen befreit gewesen war. Das Ekg des Vaters war kurz nach der Geburt des Kindes o. B. (in der Ruhe, nach Tiefatmen und Carotisdruck sowie nach Treppensteigen).

Die Mutter wurde ca. 12 Stunden vor dem Partus aufgenommen. Während dieser Zeit waren die kindlichen Herztöne abwechselnd sehr frequent (über 200 pro Minute) und langsamer (80—120 pro Minute), manchmal auch ungleichmässig. Man fasste dies zunächst als Zeichen drohender Asphyxie auf, da aber der Kopf noch nicht im Becken stand, konnte kein Eingriff vorgenommen werden. Als die kindlichen Herztöne mehrere Stunden lang dieselbe Tendenz zur Unregelmässigkeit hatten erkennen lassen, begann man jedoch den Verdacht zu hegen, dass

es sich um etwas anderes als Asphyxie handle, und man liess deshalb die Entbindung spontan ihren Lauf nehmen.

Normale Entbindung, 4 Wochen eher als berechnet. Geburtsgewicht 2 500 g. Keine Zyanoseanfälle. Während der ersten Tage in der Entbindungsanstalt wirkte das Kind ganz normal, abgesehen von einem zunehmenden Ikterus und einer hohen Herzfrequenz. Ekg ergab Vorhofflattern mit Herzfrequenz A. 440, V. 220.

Das Kind wurde am 10.6. 44 in das Sachs'sche Kinderkrankenhaus verlegt (J.-Nr 445).

 $\overline{Aufnahmebefund}$: Lebhaftes, hochgradig ikterisches Kind in völlig normalem Allgemeinzustand. Lippenfarbe o. B. Keine periphere Zyanose, keine Dyspnoe, keine Ödeme. Skelett: Schädel hart. Grosse Fontanelle 1 $^{1}/_{2} \times 1$ $^{1}/_{2}$ cm. Kopfumfang 32,5 cm, Brustumfang 31 cm, Länge 47 cm. Lungen o. B. Herz: Keine Vorwölbung der Herzgegend, kein Frémissement. Spitzenstoss nicht palpabel. Äusserst hochgradige Tachykardie mit einer Herzfrequenz von ca. 250 Schlägen pro Minute. Anscheinend einzelne unregelmässige Schläge. Bauch: Weich. Leber knapp 2 Querfinger, Milz kaum 1 Querfinger unter dem Rippenbogen palpabel. Nabel o. B. Reflexe: Pupillen- und Patellarreflexe o. B.

Laboratoriumsuntersuchungen: Hb. 121 %. Prothrombinzeit 33 Sekunden, Kontrolle 32. Urin frei von Eiweiss und Zucker. Sed. o. B.

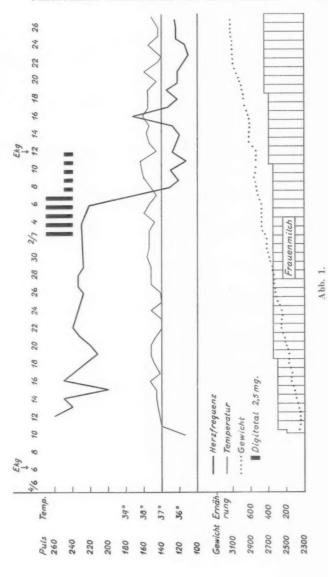
Temperatur, Herzfrequenz (mittels Stethoskops am Herzen bestimmt), Ernährung und Gewicht werden aus dem Diagramm (Abb. 1) ersichtlich. Ekg s. Abb. 2 u. 3. Röntgenuntersuchung von Herz und Lungen am 13.6. und 14.7. ergab normalen Befund.

Der Allgemeinzustand war während des ganzen Krankenhausaufenthalts sehr gut. Bis auf einen allmählich abnehmenden Ikterus war die allgemeine Hautfarbe gut. Appetit gut. Über den Lungen hörte man nie pathologische Geräusche. Die Milz war später nicht mehr tastbar, der Leberrand war 1 Querfinger unter dem Rippenbogen zu fühlen.

Am 3.7. wurde die Behandlung mit Digitotal-Astra per os 3mal tägl. 1 Tropfen (= 3mal 2,5 mg) eingeleitet. Das Flattern wich nach 5 Tagen einem normalen Rhythmus, und die Herzfrequenz, die vorher bei etwa 220 gelegen hatte, sank auf 130 pro Minute. Die Digitalisdosis wurde da auf 1mal tägl. 1 Tropfen herabgesetzt, und nach weiteren 5 Tagen wurde das Mittel ganz weggelassen. Im Anschluss daran hörte man ein schwaches systolisches Geräusch und einen klappenden ersten Ton über der Herzspitze. Im weiteren Verlauf waren aber die Töne rein.

Die Herztätigkeit blieb in der Folge normal. Rückfälle von Flattern oder Arrhythmie waren nicht zu konstatieren. Das Kind wurde geheilt und als ausschliesslich Brustkind am 30.7. 44 entlassen. Wiederholte poliklinische Nachuntersuchungen mit Ekg und Röntgen ergaben normale Verhältnisse.

Bei der letzten Nachuntersuchung am 5.10. 45 befand sich das Kind in einem geradezu glänzenden Allgemeinzustand. War bis auf ver-



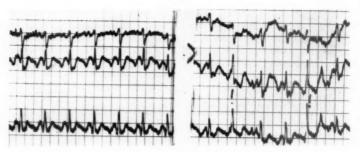


Abb. 2.

Ekg 6.6. 44: Flattern mit einer Wellengeschwindigkeit von 440 pro Minute und einem Kammertakt von 220, mithin regelmässige Blockierung 2: 1. Der Kammerkomplex macht eine physiologische Rechts-Hypertrophie ersichtlich. T 1 ist fast ausgelöscht. T 3 verschwindet in den Flatterwellen. In einem anderen Kurvenabschnitt ist die Blockierung manchmal wechselnd (BJERLÖV).

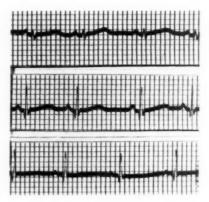


Abb. 3.

Ekg 12.7. 44. Leichte Sinusarrhythmie, 110 Schläge pro Minute. A-V 0,10 Sekunden. Initialkomplex o. B. Überwiegen des Rechtskardiogramms. T 1 positiv, T 2 positiv. T 3 isoelektrisch. Für das Alter wahrscheinlich normales Ekg (Sjöstrand).

einzelte Erkältungen ganz gesund gewesen. Appetit gut. Gewicht 10 800 g. Gute Farbe. Turgor und Tonus o.B. Herz: Rhythmus regelmässig, ruhig. Schwaches systolisches Geräusch links vom Sternum, etwas lauter im Liegen. Blutdruck 110/75. Bauch: Leberrand am Rippenbogen palpabel. Urin o.B. Röntgenuntersuchung von Herz und Lungen: o.B. Ekg ohne pathologische Veränderungen.

Es handelt sich also, um es kurz zusammenzufassen, um einen Fall von angeborenem Flattern bei einem neugeborenen Kinde junger, gesunder Eltern, bei dem Unregelmässigkeiten des Herzrhythmus schon vor dem Partus konstatiert worden waren. Das Elektrokardiogramm ergab eine im grossen und ganzen regelmässige Blockierung 2:1 mit einer höchsten Herzfrequenz von A. 440, V. 220. Vier Wochen lang hatte das Kind eine Herzfrequenz von ca. 220 Schlag pro Minute, dabei einen nicht im geringsten beeinträchtigten Allgemeinzustand und keine Inkompensationserscheinungen. Dann wurde die Digitalisbehandlung in einer Dosis von 3mal tägl. 2,5 mg eingeleitet. Nach fünftägiger Behandlung wurde der Herzrhythmus normal; die Dosis wurde da auf 1mal tägl. 2,5 mg verringert und das Mittel nach weiteren 5 Tagen ganz ausgesetzt. In der Folge wurde kein Rückfall beobachtet.

Bemerkenswert ist in diesem Fall, dass das Herz des Kindes diesen hohen Rhythmus 4 Wochen lang aushalten konnte, ohne dass Anzeichen eines Versagens der Herzkraft erkennbar wurden. Es ging vielmehr dem Kinde ausgezeichnet: es trank gut, nahm zu und wies keinerlei Krankheitserscheinungen auf. Ferner bedeutet der Fall eine Warnung davor, alle Unregelmässigkeiten der kindlichen Herztöne als Zeichen der Asphyxie aufzufassen. Dies ist besonders dann verfehlt, wenn die Arrhythmie im Laufe der fortschreitenden Entbindung Stunde für Stunde unverändert bleibt oder mit grösserer oder geringerer Regelmässigkeit wiederkehrt.

Die hier geübte Behandlung ist auch insofern beachtenswert, als mit einer so kleinen Digitalisdosis wie der hier angewendeten ein guter Erfolg erzielt wurde. Früher waren im allgemeinen wesentlich grössere Dosen im Gebrauch.

Zusammenfassung.

Paroxysmale Tachykardie und Flattern in den ersten Lebenswochen werden in bezug auf Ätiologie, Symptome und Therapie erörtert. Eine Zusammenstellung von 17 Fällen aus dem Schrifttum macht ersichtlich, dass der Herzrhythmus bei paroxysmaler Tachykardie im grossen und ganzen unter, bei Flattern über 300 Schlägen pro Minute liegt. Der Übergang ist fliessend. Dies könnte nach Verf. darauf hindeuten, dass zwischen den beiden Herzfrequenzstörungen in diesem Alter eher ein Grad- als ein Artunterschied besteht. Therapeutisch ist Digitalis das Präparat, welches bisher die besten Resultate geliefert hat. Bei den Fällen aus dem Schrifttum war die Digitalisdosierung oft auffallend hoch; Verf. berichtet aber über einen eigenen Fall, bei dem eine so geringe Digitalisdosis wie 3mal tägl. 2,5 mg, im Alter von 4 Wochen gegeben, ein angeborenes Flattern mit der Frequenz A. 440, V. 220 nach fünftägiger Behandlung in einen dauernden normalen Herzrhythmus umwandelte.

Summary.

Paroxysmal tachycardia and flutter in new-borns are discussed as regards aetiology, symptoms and therapy. A survey of 17 cases from literature indicates that the heart rate with paroxysmal tachycardia generally ranges below 300 per minute, and with flutter above this figure. Still, this border-line is not sharply defined. This might, in the writer's opinion, be taken to indicate a difference rather of degree than of type between both anomalies of the heart rate at the age in question. As to treatment, it is digitalis that hitherto has given the best results. According to literature, the doses of this drug have often been remarkably high. The writer, however, reports a case in which doses of digitalis as low as 2,5 mg three times daily, starting at the age of 4 weeks, after 5 days' treatment had changed a congenital flutter with the rate A, 440 and V, 220 into lasting normal heart rhythm.

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Massive Single-Dose Chemotherapy in Pneumonia in Children.

By

B. H. HESSELMAN.

In comparison to the extensive literature which has been published on the chemotherapy of pneumonia in adults, we are struck by the relatively little information which has been given about the chemotherapy of acute pulmonary disorders in children. However, it is now generally agreed that chemotherapy has actively contributed to lowering the mortality, lessening complications and shortening the period of hospitalization for children as well as for adults.

Since the introduction of chemotherapy in cases of acute croupous pneumonia in adults, the mortality has sunk to 5 % from 15—30 % earlier. It is to be noted that death has most often occured in older persons with complicating diseases, mainly cardiac.

In the case of acute pulmonary disorders in children, it is often difficult to distinguish between lobar pneumonia and bronchopneumonia, since there are clinical transitional forms which make such a distinction voluntary. In the following material, therefore, no division into these sub-groups will be made. This has also been the case in the majority of earlier publications by other authors. In the age-group of 0—2 years, however, bronchopneumonia predominates, whilst in higher age-groups both forms appear to about the same extent in the cases under observation here.

When we wish to estimate the effect, from the point of view of mortality, of various treatments of pneumonia in children,

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we must take many varying factors into consideration. Amongst these factors, the age and the type of the cases under observation are of prime importance. Before we knew of any specific treatment, the mortality of children in the age-group 2—14 was very low (3—5%), whereas various authors have given very different values for children under 2 years, as a rule between 30—60%. The values given by Scandinavian authors are seen in table I.

Table I.

		(—1 year	1	-2 years	014 years		
		No.	% of deaths	No.	% of deaths	No.	% of deaths	
LENSTRUP	1931	132	20	64	8	261	14	
FRIEDLÄNDER	1931	370	26	141	19	591	22	
LANDORF	1935	220	35	129	22	949	15	
LICHTENSTEIN	1939	45	47	-	_	208	14	
VILÉN	1942	103	40	m. van	_	625	14	

Lenstrup's, Friedländer's and Landorf's material gives an average value for 10-year periods. Vilén's is for the 5 year period 1934—38 only. The values can thus be considered to be representative, since incidental variations of years and seasons have been levelled in this way. It is of special interest to note how closely Landorf's and Vilén's figure coincide, since they both represent cases observed in Gothenburg's Hospital for Children, covering a 15-year period. Lichtenstein's material emanates from Kronprinsessan Lovisas Barnsjukhus during the years 1936—1938 and affords a valuable comparison with the material set forth here, which comes from the same district and has been handled under the same clinical supervision.

In cases of pneumonia in children, chemotherapy is applied along two lines, one that of continuous treatment with small repeated doses, and the other in the form of one massive single dose.

In continuous therapy, most authors calculate the dosage according to the weight of the patient, the usual dose being approximately 0.15 g per kg of the body weight for the first 24 hours, and approximately 0.10 g per kg of the weight during the subsequent days until the patient has been afebrile for 48-72 hours, with the customary division into smaller doses.

All the authors have asserted that the introduction of chemotherapy in continuous dosage has actively contributed to reducing mortality, and that it has lessened — although not entirely prevented — complications such as empyema, otitis or meningitis, and that it has shortened hospitalization.

Toxic side-effects of the sulphonamide drugs used are, however, noted. Amongst these are vomiting, changes in the bloodpicture in the form of anemia, leucopenia or neutropenia, haematuriea, and cutaneous manifestations (exanthema, erythema nodosum). These side-effects do not occur in any high degree,

Table II.

			0-	1 year	1-	2 years	0-14 years	
		Preparation	No.	of which deaths	No.	of which deaths	No.	% of deaths
LICHTENSTEIN	1939	Sulphapyridine	9	0	-	-	50	2
FRIEDRICHSEN	1939	30	13	0	9	1	46	2.2
TRACHSLER	1940	30	-	-		_	138	5.8
OPITZ & HERTZ BERGER	1941	30	112	16	-	_	231	9
SCHRÖDER	1942	20	77	9		-	97	9.3
Grod	1942	>>	86	12	-		123	14
VILÉN	1942	Sulphapyridine and Sulphathiazole	96	10	-	_	350	4.2
FRANK	1942	30	-	-	-	and a	250	3.6
Kronprinsessan Lovisas Barn sjukhus		29	61	3	30	0	200	2.5
SCOTT & JONES	1940	Sulphathiazole	?	3	-	-	167	1.8
FRIEDRICHSEN & Søbye	1941	30	18	0	10	0	59	0
Lewis	1944	39	-	-			127	9
VERMEHREN & VERMEHREN		Alfasol	16	0	5	0	50	0

nor are they of such a serious nature as to limit the use of the preparations to any great extent.

The mortality percentage given by various authors in cases treated by continuous chemotherapy are seen from table II.

In comparing tables I and II, we notice a considerable decrease of mortality in the cases which have been given chemotherapy. This decrease is most apparent in the age-group 0—2 years. It can be objected that the individual series in table II are small and only embrace short periods, but the decrease in mortality is too apparent to deny the deciding importance of chemotherapy.

Chemotherapy in the form of one massive single dose was introduced by Platt in 1940 with sulphapyridine. His intention was to reach a therapeutically satisfactory blood concentration during a sufficiently long period by means of one massive dose. With a massive dosage of 0.15—0.30 g per kg of body weight, according to age, with the highest dosage for children under 1, he obtained a blood concentration of over 4 mg% during at least 18 hours in 26 out of 35 cases. In the remaining 9 cases he obtained over 2 mg% during a similar period.

PLATT considered that the advantage of the single dose over the continuous treatment lay in the fact that the children could have more rest and sleep was undisturbed during the period when the illness affected them most. Moreover, it was simpler, and lessened the work of the hospital personnel, as well as occasioning less vomiting and nausea.

PLATT applied the single-dose massive treatment in 41 cases, of which two died. In 4 cases it was necessary to give continuous medication in addition to the massive single dose, in one case due to spreading of the pneumonia to another lobe. In 14 cases (37%) a secondary rise of temperature over 38° occured, as a rule on the 2nd or 3rd day after the commencement of treatment, but in two cases as late as the 6th day. This secondary rise of temperature did not affect the general condition of the patient, and all except two were afebrile after 24 hrs. He could not find any explanation of this rise of temperature, but considered that it lacked any clinical significance.

Since 4 deaths occured among 24 cases serving as controls 4-46885 Acta padiatrica. Vol. XXXIV

and treated simultaneously with continuous medication, and toxic side-effects, especially in the form of vomiting and nausea, were considerably more frequent in these cases, he considered that he could recommend massive single-dose treatment with sulphapyridine in pneumonia in children.

In Ugeskrift for Laeger, 1941, FRIEDRICHSEN and Sebye gave a detailed account of their experience of massive singledose treatment with sulphathiazole. The cases observed consisted of 70 children, compared to 59 treated earlier but during the same winter season with continuous sulphathiazole medication. The size of the massive single dose was decided in relation to the body weight, and was between 0.15-0.30 g per kg with a higher dosage for children weighing under 13 kg. The maximum dose was fixed at 4 g, and for 4 hours after the commencement of medication the fluid intake was reduced in order to raise the blood concentration. FRIEDRICHSEN and SØBYE found that the primary fall of temperature to 37° occured as quickly in the cases given massive single-dose therapy as in the controls, whereas a secondary rise of temperature — as a rule on the 2nd to the 3rd day - occured in 24 % of the former cases as against 11 % in the latter. The authors, like Platt, considered that this secondary rise of temperature lacked any clinical significance and interpreded it as »drug fever». Vomiting occured in 4 % of those receiving the single-dose treatment against 8 % of the control cases. The massive single-dose therapy was carried out a second time without difficulty. Two deaths occured amongst those having massive single-dose treatment, but none in the control cases. Since, however, these deaths occured in two infants suffering from serious congenital malformations, the authors considered that the deaths could not be laid at the door of lack of effectivity in the massive single-dose therapy.

FRIEDRICHSEN and Søbye, on the basis of the experience gained in their material, considered that single massive dose therapy with sulphathiazole was fully as effective therapeutically as continuous chemotherapy, simpler and cheaper to carry out, and produced less side-effects, and they therefore warmly recommended it.

In addition to these two detailed accounts, only very few publications dealing with massive single-dose treatment in pneumonia in children exist.

ROOSWAL, on the basis of 33 cases of pneumonia in children treated with sulphathiazole according to FRIEDRICHSEN's method, in comparison to 36 patients treated with continuous sulphathiazole medication — is of the opinion that massive single-dose treatment is somewhat inferior to continuous chemotherapy. In 15 (45%) of the patients treated with the massive single dose, a secondary rise of temperature occured. Of these only 6 could be interpreted as "drug fever". The remaining 9 cases were due to complications which necessitated subsequent chemotherapy. In the control series, secondary rises of temperature occured in 5 cases (14%); additional chemotherapy was required in 2 cases.

SIEGEL recommends massive single-dose treatment with sulphathiazole on the basis of his experience in 18 cases, of which 2 were resistant to massive single dosage and to continued chemotherapy, and is of the opinion that massive single-dose treatment is a valuable advance in the treatment of pneumonia in children.

Vollmer, Abler and Rosenberg have treated 25 cases of pneumonia in children with massive single doses of »sulfadimine»¹ with satisfactory results, but are not, nevertheless, of the opinion that massive single-dose treatment is preferable to continuous chemotherapy, except for the treatment of children in their homes, where care is not satisfactory.

The Present Writer's Own Material.

Since $^{1}/_{3}$ 1941, all cases of pneumonia, bronchopneumonia and capillary bronchitis treated in the medical wards of Kronprinsessan Lovisas Barnsjukhus have been given chemotherapeutic treatment in the form of massive single doses, either with sulphapyridine, sulphathiazole or "sulfadimin". As a rule, however, exceptions have been made for those cases which had been treated with continuous chemotherapy by the physician

¹ »Sulfadimin» a Swedish preparation (2-sulfanilylaminopyrimidine).

referring them to the hospital. In such cases, continuous chemotherapy was continued.

Up to $^{1}/_{7}$ 1945, 226 cases altogether have been treated with massive single doses. Of these 200 were pneumonia cases, and 26 capillary bronchitis. The diagnosis has been verified by radiography in 196 cases.

Ten of these cases were moribund on admission and died within 24 hours. These have not been included, since it must be considered that they were treated for too short a period for the chemotherapy to have had any effect. Four of these cases were, moreover, complicated by serious congenital malformations.

Laboratory Examinations.

Complete blood tests have been made in each case before commencing treatment, and urinanalysis has been made as soon as possible after admission. Swabs were taken in 189 cases before commencement of treatment, in order to type the pneumococci. Complete blood tests were made thereafter 2—3 times per week and white blood counts every day during the first week with differential count if the number of white corpuscles was less than 10 000 per mm³. Urinanalysis was done every other day, and special attention was paid to the presence of red corpuscles in the sediment.

Concentration of the sulphonamide drugs in the blood was determined 1, 3, 6, 12, 18, 24 and 36 hours after the inception of the massive single-dose treatment. Determinations have only been made on free substance according to FRISK's micro-method.

Clinical Observations.

Temperature, pulse and respiration have been recorded until the patient became afebrile. These controls have been made every other hour during the day, and at night only when the patient was awake. The condition of the skin was kept under observation in case of toxic manifestations such as exanthema or erythema. The ears have been examined at frequent intervals in order to detect any complications. It was originally intended to follow the progress of the patient with repeated radiological control of the lungs, but this proved to be impossible owing to lack of films. In cases, however, where the massive single-dose treatment did not have the desired effect these examinations were made.

Massive Single-Dose Chemotherapy.

The chemotherapeutics used in pneumonia cases were as follows: sulphapyridine (p. aminobenzolsulphonamidpyridinum) 18 cases, sulphathiazole »Astra» (2-sulphanilylaminothiazole) in 74 cases, and sulfadimin »Astra» (2-sulphanilylaminopyrimidine) in 103 cases.

The dosage has been calculated in relation to age and weight as follows: in administration by mouth 0.3 g per kg body weight for children under 3 years, and 0.20 g per kg body weight for others with a maximum dose of 8 g. The tablets have been well pulverised and emulged in milk or water. After inception of the massive single-dose treatment, the fluid intake has been restricted for 4 hours in order to increase the blood concentration. Thereafter liquid has been given freely.

The single-dose treatment has been given parenterally — as a rule in deep intra-muscular injection for children whose general condition was greatly affected and those under 1 year. In this case a 20 % solution of the sulphonamide drug diluted with twice the quantity of sterile physiological salt solution was used. In parenteral administration the dose has been reduced to about 0.10 g per kg body weight, since larger doses — owing to rapid and complete resorption — bring about too high blood concentration with a risk of cerebral irritation.

Result of the Massive Single-Dose Treatment.

In the 195 cases of pneumonia and bronchopneumonia treated with massive single-dose treatment, 48 cases (24%) have, for various reasons, also been treated with continuous chemotherapy. 11 deaths (5.6%) occured among the cases observed. More detailed information about the fatal cases, as well as about those requiring additional continuous chemotherapy will be given.

Temperature.

Besides the mortality figures for a large series, the time elapsing between the inception of chemotherapy and afebrility constitutes an important criterion of the effectivity of the treatment.

Of the 141 cases which reached recovery and were subjected to the single-dose treatment only, a fall of temperature to 37° occured, as a rule in the form of a crisis. In 91 cases (65 %) this was reached within 24 hours, in another 31 cases (22 %) within 48 hours, and in only 3 cases was it delayed more than 72 hours.

Table III shows the effect of the sulphonamides used in relation to the time required for the temperature to drop to 37°.

Table III

	1	Total No. of			
	24 hrs.	24—48 hrs.	48-72 hrs.	72 hrs.	cases
Sulphapyridine	9	1	1	_	11
Sulphathiazole	44	5	8	2	59
Sulfadimin	38	25	7	1	71

In so far as we can venture to draw any conclusions from so small a number of cases, we can state that massive single-dose treatment with sulphathiazole appears in general to produce afebrility more quickly than sulfadimin.

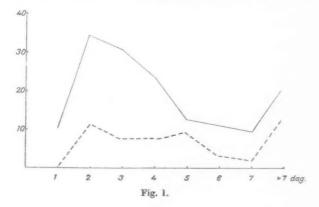
A secondary rise of temperature, as a rule on the second or the third day, occured in altogether 27 cases (14%). This rise of temperature did not affect the general condition, nor was it caused by demonstrable complications (»drug fever»). The patients all became afebrile within 24 hours without any measures being taken.

FRIEDRICHSEN'S and Søbye's observations that the fall of the temperature and of the pulse rate did not coincide, and that the pulse rate only returned to normal on the 5th to the 7th day, is confirmed in general in the cases observed here, for children under 3. In older children the fall of temperature and of the pulse rate coincide better.

Cases Which Have Required Additional Sulphonamide Therapy.

In 48 cases (24%) of the 195 cases of pneumonia treated with a massive single dose, additional continuous medication was started — as a rule on the 2nd to the 4th day. In 9 cases fever was present as well as radiological evidence of the progress of the pulmonary disorder. In 21 cases the patients still had high fever and poor general condition on the 2nd day. In 2 cases a distinct fall of temperature was, it is true, observed, but the general condition was still very poor. In 2 cases otitis had occured, in 3 cases an exudative pleurisy, in 2 cases empyema, in 1 case a lung abscess, and in one case chronic pneumonia. In 7 cases continuous medication was started, but it was shown by further examination that probably only »drug fever» was present. This happened before sufficient experience with massive single-dose medication had been gained.

The earlier massive single-dose medication can be started with relation to the onset of the disease, the better are the prospects of its producing the desired effect. This shows the effectivity of the treatment. This is shown by figure 1 in which the



inception of the treatment in relation to the day of onset of the illness is shown on the ordinate and the number of cases on the abscissa. Cases treated with one-dose medication only are marked with a straight line and those requiring additional continuous treatment with a dotted line.

Of the 48 cases which had necessitated additional continuous chemotherapy, 7 had received massive single doses of sulphapyridine (39 % of those treated with sulphapyridine), 13 sulphathiazole (17 %), and 28 sulfadimin (27 %).

Sulphonamide Concentration in the Blood.

Determination of the free substance was made in 162 cases. The maxima noted levels are seen in table IV.

Table IV.

		Nu	mber of cas	ies		
	04 mg	4—8 mg	8—12 mg %	12—16 mg %	16 mg	
Sulphapyridine massive single dose	_	1	5	2	1	
Do. + cont. chemothe- rapy	_	1	1	5	_	
Sulphathiazole massive single dose	2	14	23	1	_	
Do. + cont. chemothe- rapy	2	4		3	1	
Sulfadimin massive single dose	_	9	25	. 23	11	
Do. + cont. chemothe- rapy		4	8	10	6	

In medication per os, blood concentration attains the maximum as a rule between 3—6 hrs. after the intake of the massive single dose. In parenteral medication this occurs 1—3 hours after the dose has been given. As a rule, a sulphonamide concentration of over 4 mg% in the blood is shown after 18—24 hrs., and approximately 2 mg% after 36 hours.

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From table IV it can be seen that in the majority of the cases which have necessitated continuous medication as well as the massive single dose, the maximal blood concentration has reached a therapeutically satisfactory level, whereas the massive single dose has evidently not resulted in a sufficiently protracted therapeutically effective level, and additional continuous medication has therefore been required. In this material there is no definite difference in the blood concentration curves for the cases treated only with a massive single dose and those which have been given additional chemotherapy.

Typing of the Pneumococci.

Throat swabs for the typing of the pneumococci were taken in 189 cases. The presence of pneumococci was shown in 83 cases (42%) only, whereas Friedrichsen and Søbye found pneumococci in 78%, Vermehren and Vermehren in 60%, and Platt in 92% of the cases he observed, a difference probably caused by the fact that in the cases observed by us, throat swabs were only taken on the day of admission, whereas in the other cases, swabs were taken during each of the first three days of hospitalization. We cannot, therefore, draw any conclusion from the cases observed by us.

Mortality.

Of the 195 cases of pneumonia treated with the massive single-dose medication, 11 have died, and for the total number of cases observed a mortality of 5.6 % is registered.

The distribution of deaths in the various age groups is shown in table V.

Of the 52 children under 1 year, 9 (19.2 %) died. In 6 of these cases a pulmonary disorder occured as a complication of a serious congenital malformation or of another serious basic disease. In three infants, aged 3, 5 and 8 weeks respectively, clinical examination revealed congenital heart disease which was verified at autopsy (in two cases serious septum defects, and in one patent ductus arteriosus, besides pulmonary changes of the

bronchopneumonia type). They died on the fifth, thirteenth and seventh day respectively after the inception of treatment. It is clear that in these three cases viability was considerably lessened on account of the cardiac malformation.

Table V.

	Number of cases							
	0—1 year	1—2 years		7—15 years	Total			
Massive single dose	40	25	59	23	147			
of which deaths	5	0	0	0	5			
Massive single dose + cont. chemothe-	12	19	15	2	48			
of which deaths	4	2	0	0	6			

Two infants, aged 1 and 2 months, died respectively 2 and 6 days after admission with pertussis and bronchopneumonia without having shown any appreciable reaction to massive single-dose medication with sulfadimin.

One infant died 4 days after sulfadimin single-dose treatment, at the age of 5 days. On admission it showed signs of hydrocephalus (head-circumference $40^{-1}/_{2}$ cm) and autopsy showed pronounced internal hydrocephalus as well as bilateral aspiration pneumonia with beginning liquifaction.

The remaining three infants died 6, 7 and 11 days respectively after the massive single-dose treatment had been given, with additional continuous chemotherapy. In one case empyema developed during chemotherapy.

Of the two deaths which occured in the group 1—2 years, one case showed mongolism with congenital cardiac disease, and in the other case empyema developed during chemotherapy. No deaths occured in the age-group 3—15 years (99 cases).

If we substract those fatal cases where pneumonia occured as a complication of a serious congenital malformation or another serious basic disease, 4 fatal cases remain, which can be laid at the door of pneumonia alone. The mortality will then be $2.1\,\%$.

Complications.

In two cases which showed no physical or radiological signs of pleural exudation, empyema nevertheless developed in spite of the one-dose massive treatment, and in spite of continuous chemotherapy and pleurocentisis, both cases died. In two cases lung abscesses developed, but both recovered after additional chemotherapy. In two cases otitis developed, necessitating continuous chemotherapy.

In only one case a local necrosis developed after intramuscular massive single-dose treatment with sulphapyridine. This is a remarkably low figure with regard to the very reserved opinion towards this form of administration shown by the instructions issued by the manufacturers.

Toxic Side-Effects.

The toxic side-effects are shown in table VI.

Table VI.

	Vomiting	Microscopic haematuria	Macroscopic haematuria	Anemia	Leucopenia	Neutropenia	Exanthema	Excitation	Total no. of
Sulphapyridine	5	6	0	3	6	1	1	2	18
Sulphathiazole	14	16	0	0	12	7	1	0	74
Sulfadimin	2	28	0	6	9	5	5	0	103

The following comments on table VI can be made: In 8 cases vomiting has occured so soon after the administration of the one-dose medication that a fresh dose, either by mouth or parenterally, has been given. In the remainder of cases, vomiting has occured so late that immediate additional chemotherapy has not been given. The low frequency of vomiting after sulfadimin is remarkable. Vomiting after parenteral administration is also exceptional. Macroscopic haematuria has not been observed in any of the cases, but microscopic examination has shown a

haematuria in 50 cases. This has, however, rapidly cleared up, without leaving any signs of permanent renal injury in any of the cases.

In nine cases showing normal counts on admission, anemia with $<60\,\%$ haemoglobin has been found, with $42\,\%$ as the lowest count.

No treatment other than iron therapy has been necessary, and in all cases the haemoglobin count has been normal or has shown a higher count on discharge from hospital. Leucopenia with white count $<5\,000$ per mm³ was found in 27 cases, where leucocytosis was present on admission. It was sufficient in such cases where additional continuous therapy was necessary, to suspend the sulphonamide treatment. This was also the case for the 13 cases showing neutropenia with $<10\,\%$ neutrophil cells.

Capillary Bronchitis.

26 cases of capillary bronchitis were treated during the above period at the hospital. All cases received the massive single-dose treatment, in the form of intramuscular injection corresponding to 0.10 g per kg body weight, diluted as above.

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The cases observed are too few in number to permit of any more detailed analysis, but it should be noted that 6 cases required additional continuous chemotherapy.

9 deaths occured. 5 were admitted in a moribund condition and died within 24 hours. Two of these had complications in the form of serious congenital malformations. Amongst the others there was in one case a complication in the form of a congenital heart defect, and another showed serious signs of cerebral injury after an icterus gravis haemolyticus. In these cases chemotherapy was supplemented by strong stimulation, oxygen, and, where necessary, mustard baths.

Since such patients are as a rule in very poor general condition, difficult to feed and need as much rest as possible, there is no doubt that chemotherapy in the form of intramuscular one-dose medication in capillary bronchitis is a definite improvement from a therapeutic point of view. A comparison with 26

cases of capillary bronchitis treated previously at the same hospital with continuous chemotherapy shows practically the same mortality figures.

Summary.

An account is given of 195 cases of pneumonia and bronchopneumonia in children from 0—15 years of age, treated in the medical wards of Kronprinsessan Lovisas Barnsjukhus during the period $\frac{1}{3}$ 1941— $\frac{1}{7}$, 1945.

In all the cases chemotherapy has been given in the form of a massive single dose. In 48 cases (24 %) the massive dose treatment has been supplemented by continuous chemotherapy. Sulphapyridine, sulphathiazole and sulfadimin have been used. The dosage has been $0.3~\mathrm{g}$ per kg body weight for children under 3 years, and $0.2~\mathrm{g}$ per kg body weight for the others, with 8 g as the maximal dose.

There have been few complications, and the toxic side-effects have been extremely slight. 5.6 % fatal cases are recorded of all the cases observed, but if those cases where pneumonia has appeared as a complication of a serious congenital malformation or of a serious primary basic illness, are subtracted, the mortality is 2.1 %.

As the massive single-dose treatment is technically easy to carry out, gives the patient more repose than does the continuous treatment during the period when the illness is most severe, lessens to a considerable degree the work of the hospital personnel, gives a result which can be compared favourably with that of continuous chemotherapy, gives rise to few complications and toxic side-effects, this treatment can be recommended for pneumonia in children.

Satisfactory results have also been obtained with massive single-dose treatment in cases of capillary bronchitis.

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The Liver Function in the Newborn Investigated by Urobilinogen Tolerance Tests.

By

K. BIERING-SØRENSEN and TORBEN K. WITH.1

The etiology of icterus neonatorum is still by no means clear in spite of numerous investigations. According to recent works (e.g., Magnusson, 1935 and Vahlquist, 1940, 1941) hemolysis alone cannot explain the jaundice of the newborn, and many authors are more liable to assume that transitory liver insufficiency is its principal cause.

The liver insufficiency theory of icterus neonatorum was first suggested by Ylppö (1913) and finds some support in studies on the excretion of the bile pigments (Ylppö, 1913; Larsen & With, 1943) and in histological studies of the liver of newborn (Snelling, 1933).

Several authors have tried to solve the problem of icterus neonatorum with the aid of various functional liver tests, but up to the present without convincing results for which every new attempt at its solution may be looked upon with interest. The authors of the present paper have tried with urobilinogen tolerance tests which have not previously been used in the newborn.

Previous Investigations on the Liver Function in the Newborn.

By means of the levulose tolerance test Heynemann (1915) and Duzar & Hensch (1924) found increased excretion in several cases of icterus neonatorum, while Thompson & Wilkinson (1940) found nor-

 $^{^{1}}$ The studies presented here were aided by a grant from Froken P. A. Brandt's Legat.

mal excretion in a case with severe jaundice. Herlitz (1926) found increased values for the bromsulfalein test in infants during the first 4—5 months and especially in newborn, but no difference between the jaundiced and the non-icteric. Bossert & Loers (1925) found increased excretion in the methylene blue tolerance test in icterus neonatorum but normal values in the indigo carmine test. Lin & Eastman (1937) demonstrated that both non-icteric and jaundiced newborn react normally to the bilirubin tolerance test, and Biering-Sørensen & Dyggve (1945) found that the vitamin K sensitivity of the newborn is not correlated to the degree of the hyperbilirubinemia. Further, it is to be mentioned that the serum ciric acid concentration (Salomonsen, 1939) and the albumin-globulin quotient of the serum (Duzar & Rusznyak, 1924) in icterus neonatorum and the relation between free and total cholesterol of the serum (Sperry, 1936) in the newborn is without correlation to the serum bilirubin concentration.

Regarding all these investigations it is, however, to be remembered that the evaluation of liver function tests in the newborn is a somewhat difficult matter as comparison to the normal values found in adults is not quite correct.

A fact speaking strongly against the hemolysis theory and for the liver insufficiency theory of icterus neonatorum, and which has yet been all too little noticed, is the high serum bilirubin concentration in icterus neonatorum — on an average about 10 mg per 100 ml but reaching 50 mg per 100 ml — which far exceeds the values found in the hemolytic jaundice of adults — most often 2—4 mg per 100 ml and never above 6—7 mg per 100 ml (cf. With, 1943, 2; 1944; Larsen & With, 1943).

On the Use of the Urobilinogen Tolerance Test in the Newborn.

According to all investigations performed with a reliable technic neither the stools nor the urine of newborn contain urobilinoids (cf. Havret, 1930; Simon, 1938/39; Larsen & With, 1943). We were able to confirm this as we could demonstrate no urobilinoids in the urine of 50 newborn with or without jaundice. Consequently, spontaneous urobilinuria cannot be used as a functional liver test in the newborn and the ability of the liver to excrete urobilinoids must be investigated by means of tolerance tests.

The tolerance test with urobilinoids was introduced by WAT-

son (1936), who used stercobilin, and further developed by With (1946), who used urobilinogen, IX, α . These authors, however, only examined adults. According to With, the percentage of parenterally injected urobilinoid which is excreted with the urine during the first 3—10 hours after the injection normally does not exceed 5 % when doses corresponding to ca. 1 /₃ mg per kg body wieght are given. Watson found a pronounced increase in this excretion percentage in patients with liver disease or occlusive jaundice, but he only examined 8 patients. With found an increased excretion percentage in acute hepatitis and in occlusive jaundice but varying results in chronic hepatitis.

While in the adult the employment of the urobilinogen tolerance test is made difficult by the rather considerable spontaneous excretion of urobilinoids which may occur even in normal persons, this difficulty does not exist in the newborn, thanks to the entire absence of spontaneous excretion of urobilinoids in the latter.

As is the case with all functional liver tests the evaluation of the urobilinoid tolerance test in the newborn is difficult as we do not know to which degree functional liver insufficiency is found in the newborn and therefore only have the normal values in adults for comparison. But if one correlates the degree of jaundice with the excretion percentage of the urobilinogen tolerance test one would assume it possible to obtain information as to which degree insufficiency be the cause of the jaundice, as experiences from adults show that in more pronounced degrees of hepatic insufficiency and biliary obstruction a well-marked increase in the urobilinoid excretion percentage is found regularly in the tolerance test.

Technic of the Test.

The urobilinogen preparation described by With (1946) containing 25—50 % of urobilinogen, IX,α was employed. The

¹ We thank the factory *Ferrosan* of Copenhagen for the manufacturing of the preparation and Grosserer Frederiksen for the delivery of ox gall-stones used as raw material.

⁵⁻⁴⁶⁸⁸⁵ Acta pædiatrica. Vol. XXXIV

preparation was stored in the ice box in ampules filled with nitrogen. Immediately before each series of tests the contents of one or more ampules were weighed and dissolved in ca. 2 ml 96 % alcohol; then addition of 2 drops of 10 % NaOH and dilution to 10-20 ml with distilled water. The urobilingen concentration of the solution prepared in this way was controlled by taking $^{1}/_{2}$ ml and adding $^{1}/_{2}$ ml of benzaldehyde reagent and diluting to 10-20 ml with a saturated solution of sodium acetate; from the extinction of this solution read in the Pulfrich photometer (filter S. 53, 1/2 cm layer) the concentration is calculated (cf. With, 1942, 1; 1945; 1946). The amount of the solution containing the number of mg of urobilingen to be injected can now be calculated, and given intramuscularly into the buttocks of the infant; in our experiments doses corresponding to 1 mg per kg body weight were given, i.e., doses twice to three times those used by WITH (1946) in adults. The injections did not give rise to by-effects in any of the infants.

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In order to secure an accurate collection of the urine only boys were used in the experiments. The urine was collected in small glasses according to the method described by PORTER & CARTER (1944) during the first 6 hours after the injection; only in a few cases with very small diuresis were longer periods used. In most cases the urine was analysed before the injection and was always found to be free from urobilinoids.

The urine analyses for urobilinoids were carried out by means of the technic described by With (1942, 1945); reduction with colloidal ferrous hydroxyde was used in all cases. The serum bilirubin was determined with With's (1942; 1943, 1) modification of Jendrassik & Gróf's method.

Material.

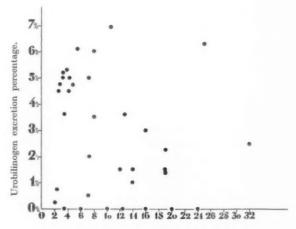
31 newborn¹, aged 1—14 days with birth weights ranging from 1 150 to 4 400 g, were subjected to the urobilinogen tolerance test; in a few infants two tests were made. A little above

¹ The authors thank Professor E. Brandstrup, M. D., Lying- in Department B of the Rigshospital for the opportunity to use the newborn in his Department.

one-half of the infants showed jaundice on the day of the test. The serum bilirubin concentration was determined in all cases and varied between 2 and 32 mg per 100 ml. Further, some infants with diseases of the liver or bile passages were subjected to the test (cf. below).

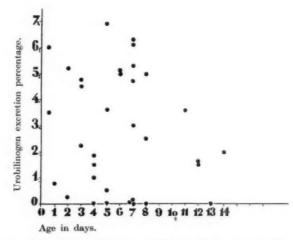
Results.

The results of our tests are seen in Figs. 1—3 in which the urobilinoid excretion percentage during the first 6 hours after the injection is placed along the ordinate axis. The excretion percentage is seen to vary considerably. In 7 of the cases — i.e., ca. 20 % — the excretion is above 5 %, but in 7 others no urobilinoid is excreted. Fig. 1 shows that there is no definite correlation between the degree of bilirubinemia and the excretion percentage, as high and low excretion percentages are found with about equal frequency with high and low serum bilirubin concentrations; in a case of severe jaundice (20—24 mg per 100 ml) no urobilinogen was excreted.



Serum bilirubin concentration (mg per 100 ml).

Fig. 1. The correlation between the serum bilirubin concentration and the excretion percentage after urobilinogen tolerance tests in newborn.



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Fig. 2. The correlation between the age and the excretion percentage after urobilinogen tolerance tests in newborn.

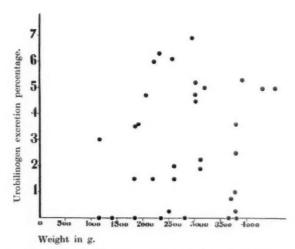


Fig. 3. The correlation between the weight in kg and the excretion percentage after urobilinogen tolerance tests in newborn.

In Fig. 2 the age and in Fig. 3 the birth weight are correlated to the excretion percentage, which seems to be independent of both.

Two of the newborn suffered from congenital syphilis — positive Wassermann reaction but no clinical symptoms — and showed excretion percentages of 4.7 and 6.1, *i.e.*, values which cannot be regarded as definitely pathological according to the observations in adults.

A few cases suffering from diseases of the liver or bile passages were tested. A 2-month old infant with congenital atresia of the common bile duct excreted in two tests 0 and 1 %, while another infant with the same anomaly excreted 45 and 63 %. At the autopsy both infants showed cirrhotic changes of the liver which were more pronounced in the infant with the high excretion percentage. A 3-month old infant with congenital cirrhosis of the liver showed only an excretion of ca. 1 % in several tests, and a 1-month old infant with severe gastro-enteritis complicated by hepatitis showed no excretion in spite of the fact that it died from intoxication the day after the test.

Discussion.

The urobilinogen tolerance test in newborn is thus seen to give results that vary greatly from one individual to the other, and the variations do not seem to be correlated to the functional capacity of the liver. The fact that some infants with severe liver damage only show a very low excretion percentage may be explained by a high kidney threshold for urobilinogen in these cases — an assumption which is not quite unlikely as an abnormally high kidney threshold for bilirubin in the newborn was found by LARSEN & WITH (1943) and a relative insufficiency of the kidney of the newborn was demonstrated by McCance & Young (1940). If one assumes that the relative kidney insufficiency and the threshold for urobilinogen varies individually it is also possible to understand that the urobilinogen excretion percentage may vary considerably.

As the real urobilinogen excretion percentage probably is

somewhat higher than found by us — owing to the fact that some urine may have been lost — and as ca. 20 % of our newborn showed excretion percentages above the upper limit for normal adults, our results point in the direction of the existence of a moderate relative insufficiency of the liver in the newborn.

Summary.

To elucidate the etiology of icterus neonatorum which is still obscure urobilinogen tolerance tests were performed on 31 newborn and a few infants with diseases of the liver and bile passages. The technic of WITH (1946) was used. The results of the investigation point towards the existence of some degree of liver insufficiency in the newborn, but they are difficult to evaluate as the test is also influenced by other factors than the liver function, presumably the kidney function. The test is consequently of no use as a functional liver test in infants.

Attention is drawn to the fact that the serum bilirubin concentration in icterus neonatorum is much higher than in the forms of hemolytic jaundice in adults, which speaks against the hemolytical theory of the origin of icterus neonatorum.

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On some Anemias in early Life.

By

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Our knowledge of congenital anemia is handicapped by the fact, that of the majority of the cases described in literature we are not sure whether the anemia was actually congenital. The morphological bloodfindings and anatomopathological data, if any, generally have regard to an age of some days, even of some weeks after birth. Some writers on congenital anemia even stress the fact of the children's »normal ruddy appearance» at birth. The Abbott's1 for instance say this of their case 1. The bloodexamination on the first day of life, however, showed a hemoglobin percentage of 82 %, a number of red corpuscles of 4.136 000, of white of 13 600. These values are certainly too low for a normal newborn infant. In their patient the pallor became remarkable only on the 15th day of life. Yet the family anamnesis indicated the child's illness as pertaining to the trias hydrops foetalis, icterus gravior and congenital anemia and not to the anaemia temporaria or allergica of LEHNDORFF2, which will be mentioned later.

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Further it is often difficult to state whether in cases where no erythroblastemia was found during life and at the post mortem no erythroblastosis, these were really lacking or that perhaps they might have existed over a certain lapse of time. Their pre-

¹ K. H. Abbott a F. F. Abbott: Am. J. D. Ch. 49, 724, 1935. We do not intend to give a full review of the literature, but merely propose to cite some observations to illustrate opinions defended in the text. More-over one must take into consideration our five years isolation in the war.

² H. LEHNDORFF: Anemia neonatorum. Ergebn. d. inn. Med. u. Kinderhk. 52, 611, 1937. — H. LEHNDORFF: Archiv f. Kinderhk. 113, 102, 1938.

sence is generally regarded in favor of the case being one of the trias, but their absence certainly has not the same value in the contrary sense.

By a number of serial blood examinations in icterus gravior we ourselves have learned that during the first days of life a considerable erythroblastemia may be present, which on the following day has practically disappeared. It may also occur, though seldom, that the nucleated red corpuscles appear again in the bloodstream after they had already left it and finally they may be absent during the first days of life and make their appearance later on. As examples of the above the following observations may be cited. Under the title of »Anemia of the newborn and erythroblastosis are they inseparable?» Philip Cohen¹ relates a case of severe anemia without icterus and without erythroblastemia. The first blood examination was made on the sixth day of life and 1 normoblast on 100 leucocytes was found. There is a possibility, that in an earlier examination a much larger number might have been found. In his second observation which he terms »icterus gravior without anemia» (though on the second day of life the value of hemoglobin was only 92 %, of red blood corpuscles 3 690 000 of white 23 900) he found 23 000 normoblasts per mM; on the 6 day the nucleated red corpuscles had almost left the bloodstream. In Mannheimer's2 case of congenital anemia the nucleated erythrocytes numbered on the fourth day of life 1/2 % of the white ones, on the ninth day their number was 212/3 % and signs of hyperactivity of the bone marrow were apparent. The same process for the nucleated red corpuscles in circulation probably holds true for the extra-medullar formation of them, the erythroblastosis. One of the present writers3 has described nuclear icterus with and without erythroblastosis. The observation without erythroblastosis concerned one of twins; in examining the blood on the second day of life the nucleated red cells proved totally lacking, nor were the large forms of erythrocytes present with more or less basophilic staining, which

¹ Philip Cohen: The Journal of Pediatrics 7, 220, 1935.

² E. Mannheimer: Acta Paediatrica 18, 237, 1936.

³ C. DE LANGE: Jahrb. f. Kinderhk. 145, 273, 1935.

otherwise are a constant finding in the neonatal blood. Post mortem there proved to be no extra medullar blood-formation. the bonemarrow showed activity. The other child survived; here the nucleated bloodcells were also absent at first, but on the 13th day of life 6 normoblasts on 100 leucocytes were found, there were also immature erythrocytes. This child afterwards developed neurological symptoms caused by nuclear icterus.

The above cited facts show the importance of the time factor, which de Lange has already laid stress upon in the publication mentioned at foot. There are cases known of hydrops foetalis universalis (typus Schridde, therefore belonging to the trias) without erythroblastosis or without erythroblastemia. The patients with hydrops almost always die very shortly after birth, but very exceptionnally they may survive and develop normally as the observations of Shapiro and Cohen¹, of Maharik² and of Salomonsen³ prove, but to ensure the possibility of hydrops congenitus without erythroblastemia, there ought to be the certainly extremely rare observation of a child surviving with hydrops, in which the nucleated red bloodcells were lacking on the first examination and did not appear later on.

As for the erythroblastemia in congenital anemia it is known that the nucleated red elements may disappear after a blood-transfusion. It is also possible that nucleated red cells are found in the bloodstream, but that post mortem no extra-medullar hematopoiesis is found; the contrary has also been stated (MAC CLURE). If the extra medullar bloodformation is lacking and there are nevertheless nucleated erythrocytes in the circulation, one would expect them to be only orthochromic normoblasts and not more immature stadia. Rohr stated that nucleated red cells cannot escape from the bone marrow as they do not possess amoeboïd movements and so cannot reach the capillaries. Van Buchem and Botman's, however, on the grounds of clinical and anatomo-

¹ L. M. SHAPIRO a Ph. COHEN: Am. J. D. Ch. 58, 1050, 1939.

² J. Maharik: Annales Paediatrici 155, 107, 1940.

³ L. Salomonsen: Acta Paediatrica. Vol. XXXII, 110, 1945.

⁴ Mac Clure: Zeitschrift f. Kinderhk. 51, 86, 1931.

⁵ F. S. P. VAN BUCHEM a TH. BOTMAN: Nederl. Tydschrift v. Geneesk. 83, 4022, 1939.

pathological findings, opine that this does not hold good for orthochromic normoblasts whose appearance according to these writers, is connected with an insuffiency in the reticulo-endothelial system.

In performing anatomo-pathological examinations of foetus or of children who were born à terme, but who died after a few days, from families with polyletality caused by the trias syndroom, a marked erythroblastosis is frequently found; symptoms of hydrops, icterus or anemia lacking or still lacking, but the liver and the spleen often being enlarged (v. Gierke¹, Ferguson², de Lange³, Salomonson⁴). Not all these observations clearly prove the trias syndroom being present e.g. case 4 of Ferguson concerning a second child which dies one hour after birth. Erythroblastosis is found, but no hydrops and no icterus. The first child was healthy. We are entitled however to suppose that the tragedy began with the second child.

There are in the literature various publications on congenital anemia, where the reader wonders why they are not described as anemia following on icterus gravior. This holds true, for instance, of Ecklin's case which is generally cited as the first described case of congenital anemia. Mannheimer (l. c.) holds the same opinion.

In diagnosing erythroblastemia it is essential, to know how many nucleated red cells may be in the circulation of the newborn without his being abnormal. Opinions differ widely. Montfort and Brancati⁶ say that at birth the number of nucleated red cells is 5 per 100 leucocytes, the number falling below 1 % already on the second day of life. Krost⁷ on the contrary gives as normal values for the new-born 2—30 %. We ourselves once found 22 % of the white cells, the child exhibiting nothing abnormal.

¹ E. v. Gierke: Virchow's. Archiv 275, 330, 1929.

² John A. Ferguson: Am. J. of Path. Vol. VII, 277, 1931.

³ C. DE LANGE: Acta Paediatrica 13, 292, 1932.

⁴ L. Salomonsen: Z. f. Kinderhk. 51, 181, 1931, and Acta Paediatrica 18, 357, 1936.

⁵ Th. Ecklin: Monatschr. f. Kinderhk. 15, 425, 1918.

⁶ J. A. Montfort a G. J. Brancato: Arch. Ped. 52, 431, 1935.

⁷ G. N. Krost: J. Ped. XVIII, 357, 1936.

The cases of erythroblastosis (better said erythroblastemia) which Salomonsen describes and which he calls erythroblastosis neonatorum temporaria evidently belong to the trias.

Those forms of congenital anemia in which nucleated red cells do not appear in the circulation and in which after death no signs of extra-medullar blood-formation are found, are by several writers termed aplastic forms. This, however, is only allowable as also the bone marrow proves inactive, as has been stated in very few cases as yet (Pasachoff and Wilson).

The observation of Brown, Morrison and Meyer² does not stand out very clear. Their patient showed extreme pallor on the 6th day of life. Examination of the blood yielded a value for hemoglobin of 50%, red blood cells 2 500 000, white 60 000, moderate shift to the left (myelocytes, metamyelocytes, bandforms). No foci of bloodformation in liver, spleen or kidneys, no siderosis, no activity of the bone marrow according to these writers. As the diagnosis of the pathologist, however, they cite shyperplasia of the bone marrows, definite hyperplasia of the granulocytic element with proportional increase in the number of eosinophils, no evidence of increase in erythroblasts. At the post mortem the bloodplasma proved to be yellow.

The afore said proves in how large a measure the presence, or absence, of nucleated red bloodcells in congenital anemia, icterus and hydrops may be a question of time. Only a daily blood-examination allows any conclusion being drawn. It also proves that the three forms in which the trias-syndroom may appear are seldom pure forms.

One might propose the following scheme: it must be borne in mind, however, that only the status at a definite moment is meant (time-factor).

- I Those cases in which either hydrops, ieterus or congenital anemia is prominent.
- ${\bf II}\,$ Mixed forms (the first word indicates the main diagnosis).

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- a hydrops with icterus.
- b hydrops with anemia.

¹ H. D. PASACHOFF & L. WILSON: A. J. D. Ch. 49, 411, 1935.

² S. S. Brown, M. Morrison a D. A. Meyer: A. J. D. Ch. 48, 335, 1934.

- c icterus with edema.
- d icterus with anemia.
- e anemia with edema.
- f anemia with icterus.
- g cases where the whole trias is present.
- III erythroblastemia without anemia, icterus or hydrops.
- IV congenital anemia without erythroblastemia, icterus or hydrops.

The measure in which the granulocytic system participates in the trias differs widely. The leucocytosis often goes far beyond that of the newborn; immature forms (myelocytes, metamyelocytes) occur in increased number. Several times we also observed myeloblasts in the blood stream in icterus gravior. In many cases the name of erythro-leukoblastosis (blastemia) will without any doubt be the proper to apply.

Whether a congenital anemia belongs to the trias may be ascertained from the anamnesis. Generally, but not always the first child is exempt and a congenital anemia in the second child may be the first manifestation. Several writers mention cases in which three or more healthy children were born before a child with the disease appeared (Leonard 9th child).

For a couple of years it has been known² that a woman lacking the Rh-factor in her blood and bearing a Rh-positive foetus in utero, will probably give birth to a child belonging to the trias, should she have formed a sufficient quantity of anti-Rh-immune-bodies (iso-immunisation). Lesions in the placenta, however, must be present.

In cases where the origin of the congenital anemia is doubtful a test of the mother's blood may afford a solution. Nursing by the mother is not advisable (Hellman and Irving³, Ziegler⁴).

In general the hypothesis of mother Rh-negative, foetus Rh-positive producing erythroblastosis in the child, has been favourably

¹ Martha F. Leonard: The Journal of Ped. 27, 247, 1945.

² References in the article of BIRGER BROMAN. Acta Ped. 31, 275, 1944 a 31. Suppl. II, 1944.

 $^{^{3}\,}$ Hellman a Irving quoted after H. R. Litchfield: J. Ped. 27, 352, 1945.

⁴ E. Ziegler: Annales Paediatrici 165, 168, 1945.

recieved, though the question is certainly not fully solved. So RANSTRÖM¹ in his critical article lays stress on the insular hyperplasia of the pancreas, on the adreno-cortical hyperplasia found in some cases and on his own finding of basophilic cells in the hypophysis, normally lacking in neonati. He therefore advocates a hormonal treatment in the child with erythroblastosis, which already DE Snoo has advised in giving large doses of menformon directly after birth and in the first days of life. However, he also attributes a rôle to the iso-immunisation of the mother.

There is another form of anemia in early life which must be briefly discussed. By Lehndorff (l. c.) it is called anemia neonatorum or allergica. Infants of this form of anemia become markedly pale, though not before the end of the first week of life, and every one who has observed these children is struck by the fact, that while possessing a hemoglobin tax of only 20-40 %, they behave like normal children. They take their food, they move, yawn and sneeze like ordinary infants as a rule without any dyspnoe. In most cases the blood has a high colour index and the morphological picture is aregeneratory. By puncture of the bone marrow Lehndorff, however, stated an activity of the marrow, but sometimes the blood resembles that of the anemia pseudoleukemica infantum, or that of an erythroblastemia. This form of anemia has a favourable pronostic, whereas the mortality of the trias-anemia is still 12 % according to the literature on the subject.

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JOHANNA STALLING-SCHWAB² has described in the Dutch literature five cases (two concerning twins) in which the infants were not anemic at birth, at least not clinically, but all of whom grew more or less seriously anemic between the 10th and the 21st day of life. The blood picture was partly without a shift to the left, without immature forms in the red and white bloodcells, partly resembling that of von Jaksch-Hayem Luzet's anemia. Also the picture of congenital erythroblastemia was found with

¹ S. Ranström: Acta Ped. Vol. 33, fasc 1, 1945.

² JOHANNA STALLING-SCHWAB: Maandschr. v. Kindergeneesk. 6, 487, 1937.

high values for nucleated red blood cells in all their varieties. All the children recovered and the anamnesis was negative concerning the trias, but it must always be borne in mind, that the children who presented the erythroblastosis might have been the first ones manifesting the trias.

Some writers ascribe this form of anemia to a deficiency illness of the mother which in all probability is not right. Lehndorff is inclined to regard it as a kind of shock-pregnancy-reaction after Mayerhofer's allergic theory, quod est ad demonstrandum. Lehndorff opines that it is better to drop the name of congenital anemia once for all, as there are so few observations as to the status of the blood immediately after birth and anatomo-pathological findings in early life are almost entirely lacking. He proposes to use the name of anemia neonatorum.

Is there a clear difference between the congenital anemia of the trias and Lehndorff's anemia with a negative anamnesis ad hue? v. Reuss¹ is inclined to accept transitional forms. The solution lies in the future; sufficient data not being yet available. If the anemia which appears after \pm a week really belongs to the trias, if it may be regarded as a mild form of this syndroom, one might expect that in the mother's blood anti-Rh-immunebodies might be found.

If a child with congenital anemia dies from an intercurrent illness and a post mortem is not permitted, a microscopical examination of the placenta as well as an examination of the mother's blood can be of use, as Goormagtigh² found in hydrops congenitus foci of bloodformation in the placenta. This, however, holds good only in case the child is already pallid at birth and the attention of the physician is drawn to the possibility of the trias. With the knowledge that hydrops, icterus and anemia are only different forms of the same anomaly and that children may recover from all of them, Goormagtigh's opinion that hydrops congenitus is a variety of leukemia, strikes us as curious. He adds: »l'étiologie de cette variété de leucémie ne sera éclaircie que le jour, ou le sera celles des autres. Ce sera l'oeuvre de demain.»

¹ A. v. Reuss: in Erg. Bnd. Pfaundler u Schlossmann, 1942.

² N. GOORMAGTIGH: Annales d'Anatomie pathologique méd. chir. II, 413, 1925.

That congenital (sensu strictiori) anemia really occurs and that it has a right to a name of its own is proved by the following observations.

Family A. The first child of healthy parents with negative reaction of Wassermann and Sachs-Georgi is born with spinal bifida and dies after three weeks. This child was not markedly icteric nor for a longer period than is the case in normal icterus neonatorum. The second child is two months premature and born with hydrops universalis. This child lived only for a few hours, there was no regular breathing, now and then a gasp was heard. The examination of the blood was performed by one of us (T. Janssen), one hour after birth; hemoglobin 38 %, red blood cells 1 380 000 (anemia with hydrops), white cells 6 800, differential eos 1, myelocytes 3, metamyelocytes 3, bandforms 10, polynuclears 48, lymphocytes 36, monocytes 1 on 100 leucocytes and 182 nucleated red cells (macroblasts and normoblasts); anisocytosis and polychromasia.

The third child dies within ten minutes after birth, was extremely pale. The post mortem is performed by Dr. E. F. J. H. FALGER in Zaandam. Rigor mortis, small blue spots scattered over the skin. Lungs not ventilated. The heart larger than the child's fist, no anomalies of vessels, valves or septa. The liver is much enlarged (weight 275 g, normally \pm 135 g), almost filling up the whole of the abdomen, on section nothing abnormal shows. The spleen is also much enlarged, weighing 60 g (normally \pm 8 g), on section no anomalies. The other visceral organs look pale but macroscopically normal. The weight of both adrenals together is 4.5 g.

In a smear of the heart's blood a large number of nucleated red bloodcells is found.

The organs are transported to the Laboratory of the Emma-Hospital for sick Children in Amsterdam for further investigation.

The brain shows normal convolutions; on its being divided into vertico-frontal slices a dilatatio cavi septi pellucidi appears (fig. 1 a 2), the first child having suffered from a spina bifida. The brain is so pale in colour that no marked difference is visible between the cortex and the medulla. No hemorrhage, no embolus, no thrombosis is found. An inspection of those parts of the cere-

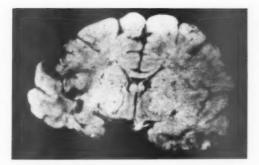


Fig. 1. Frontal part of cavum septi pellucidi.

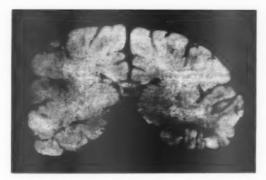


Fig. 2. Caudal part of cavum septi pellucidi.

brum which especially suffer in nuclear icterus, shows that a yellow discoloration is entirely absent.

Microscopical examination.

Parts of the organs are embedded in paraffin and stained with hematoxylin-eosin, after VAN GIESON, TURNBULL-HUECK (iron) and DOMINICI (bloodcells).

Liver. The radiar configuration of the livercell-columns is almost irrecognizable, the cells being pressed together or separated from one another by a large number of foci of bloodfor-

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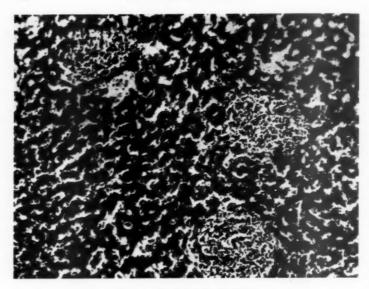


Fig. 3. Bloodfoci in the liver.

mation (Fig. 3). No vacuolization of the liver cells. Kupfer's cells are not swollen and their number has not increased. In some spots the bloodcapillaries are wide and contain numerous nucleated red cells, elsewhere their lumen is almost obliterated by the pressure of the bloodformation foci. These latter are generally found in the capillary sinus. One is struck by the different aspects of these foci. Some are rarified consisting of small cells with pyknotic nuclei and a very small protoplasmic border. They much resemble small lymphocytes, but must be regarded as immature red cells (SCHRIDDE); some are slightly more mature and show karyorhexis; these foci contain scarce myelocytes. Another form of foci consists of larger cells with more leptochromic nuclei; here the protoplasma is broader. The cells are more packed together and the clumps of these cells are apparent in the microscopical preparations. Sometimes in a rarified focus a group of the latter cells is situated. In all probability these cells are lymphoblasts. Especially under the liver capsule the foci of blood-

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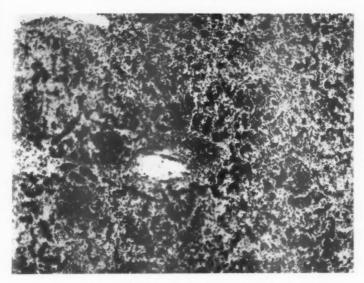


Fig. 4. Iron stain of the liver (the iron shows black in the picture).

formation form an almost diffuse area, where only single livercells are recognizable. The walls of the bloodvessels are for a large part infiltrated with small cells; in some spots there is a slight reticular diffusion of these cells round the bloodvessels. The connective tissue in the espaces-porte also contains small round cells and they are also seen there in the wall of the bloodvessels and of the bile ducts. In contrast to our findings in icterus gravior the myelocytes are lacking in the portal canals. Bilethrombi are nowhere to be seen. The iron stain reveals a marked siderosis (Fig. 4), the livercells partly showing blue pigment, partly diffuse blue colouring. The capsule is almost without iron. The adventitial layer of the bloodvessels is in some spots of a faint blue colour. The bile pigment in the liver is not increased.

Spleen. The histological picture of the spleen has completely changed, the Malpighian bodies have almost disappeared; here and there remnants are visible in connection with bloodvessels. The sinus have a normal width, the endothelium not being swollen.

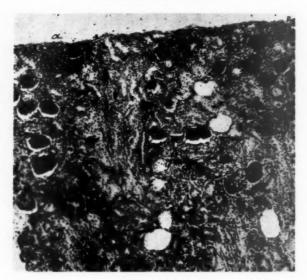


Fig. 5. & Bloodfocus underneath the capsule of the kidney.

In some places the sinus contain clumps of cells with leptochromic nuclei of the same aspect as occurring in the liver and which we regard as lymphoblasts. Myelocytes are not found; this also in contrast to the spleen in icterus gravior according to our investigations. The siderosis of the spleen is but slight; the capsule, however, shows like a small blue band. Some trabeculae and the adventitial layer of some bloodvessels have a faint blue tinge.

Kidney. Beneath the capsule and in the connective tissue of the bloodvessels a moderate number of foci of bloodformation is visible. They consist of small round cells with pyknotic nuclei and almost without protoplasma. The glomerular and the tubular systems are intact. The tubuli do not contain any bilecasts. On staining for iron an almost elective blue staining of the tubuli contorti can be seen (as also has been observed by one of us in some cases of icterus gravior). (Fig. 5 a 6.)

Comment. There can be no doubt that the anemia in this case was strictly congenital. The question arises, whether a mixed

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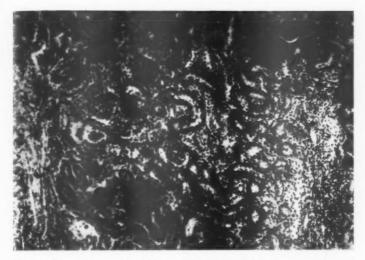


Fig. 6. Iron stain of the kidney. The tubuli contorti showing black in the picture.

form of anemia with icterus might have developed if the child had not died. This eventuality cannot be ignored; a high degree of blood destruction might have led to a hemolytic and by pleiocholia to an mechanical icterus. If so, the jaundice ought to have been manifest at birth and not some days after birth as the normal icterus neonatorum. In our opinion the fact that bile thrombi were lacking and that the bile pigment in the liver cells had not increased contradict to a certain degree this possibility.

Also in the following case there is small doubt that the anemia was a genuine congenital.

Family B. New born child. Dr. J. was called in, but on arriving found the child already dead. The midwife, however, who supervised the partus, related that she was struck by the extreme pallor of the skin, the mucous menbranes being also markedly pale. The latter circumstance is highly important as regards the differential diagnosis between anemia and asphyxia pallida. The anamnesis showed that the first child was still born and one month

premature, the second two months premature and also still born, then followed two abortions of 6 months, then the above mentioned infant was born. On examination directly post partum it was stated that the liver reached to 4 finger's breadths below the costal margin, the spleen being also enlarged. The WASSERMANN-reaction in the parents proved negative, the mother being Rhnegative, but anti-Rh-immunebodies lacking in her blood.

The third observation is one by DE SNoo¹, cited after the Dutch publication. Family C. In this family the first child was born weighing 4 000 g. There is asphyxia and the child does not come to. The partus was normal and à terme. The second child was born in 1938, the weight being more than 4 000 g, but it was macerated. Then in 1941 a normal child was born, which developed normally. The next confinement ends in the spontaneous birth of a child of 3 680 g. This child at birth has a bluish white colour and shows blue spots on the skin. Bloodexamination immediately after birth yielded the following data: hemoglobin percentage 59 %, red cells 2 260 000, on 100 leucocytes 166 nucleated red cells. The hemoglobin slowly rises. The mother having developed a thrombosis, the child remains 10 weeks in hospital. On discharge the hemoglobin is 77 %, the child's weight is 5 700 g. The anamnesis proves this case also to belong to the trias.

The fourth observation is by VAN TONGEREN² also published in the Dutch literature. It concerned the first pregnancy of a woman aged 39 years. The partus was spontaneous, weight of the child 2 790 g, length 51 cM. The infant was markedly pale. Hemoglobin percentage 25 %, red cells 1 260 000, white 23 300. On 100 leucocytes 204 nucleated red cells were counted. The child died a few hours after birth, before a bloodtransfusion could be given.

Anemia e causa ignota.

Fanconi³ has rightly stated that there is no scheme that covers all anemias. This is once again proved by the following observation.

¹ K. DE SNOO: Ned. T. v. Verlk. en Gyn. 1941, 3.

² F. C. v. Tongeren: Ned. T. v. Verlk. en Gyn. 1945, 4.

³ G. FANCONI: Monatschr. f. Kinderhk. 68, 129, 1937.

The child D. is brought to the outdoor department of the Emma-Hospital for sick Children in Amsterdam in a disstressing state. The child's age is 2 1/2 months, she is the 6th child in the family, one had died from a cerebral disease and one of enteritis. The patient has been nursed over a period of 2 months, for a short time supplementary food had been given, then stopped again. The child cries frequently especially if moved. The diapers are wet in an ordinary way, the stools are normal, only in the last days rather greenish. There is a slight cough, but the whole family has taken a cold. The anamnesis gives no more particulars to explain the miserable state of the child. The patient is admitted to the hospital and the following status is taken. Small, badly cared for infant with remnants of eczema, extremely pale with slight cutaneous hemorrhages. No finding in heart and lungs. There is a marked dyspnoea. No mikropolyadenia. The liver does not appear to be enlarged, but the spleen is. Urine: albumen positive, sugar negative, in the sediment numerous granular casts, some leucocytes and erythrocytes. Blood: Sahli 15 %, red cells 954 000, white 3 700. Differential: polynuclears 5.3, lymphocytes 91.6, monocytes 21, Türk's cells 1 %. Anisocytosis, slight poikilocytosis. The major number of the leucocytes belong to the very small forms; some larger ones show azurophilic granules. In examining the smears one normoblast is discovered. The polynuclears show degeneration.

On taking blood for Sachs-Georgi's reaction, which proves negative, a lipemia of the serum is found.

Although seriously ill, the child took her bottle well, she became very hoarse and the respiration developed Kussmaul's typus.

After a stay in the hospital of only 1 $^{1}/_{2}$ days, death supervened. Post mortem (Dr. J. C. Schippers).

The corpse is extremely pallid, there is a little edema and slight cutaneous hemorrhages. Both pleural cavities contain a small quantity of free fluid, also the fluid in the pericardial cavity has somewhat increased. In the apex of left lung there is a patch of gelatinous appearance with a bluish red colour, where the tissue is more firm than in the surrounding parts. Some hypostasis in the lower lobe of the right lung. The heart has somewhat increased in size and its consistency is flabby; valvulae, septa and large bloodvessels intact. No enlarged glands in thorace.

Spleen much enlarged, weight 65 g, dimensions $10\times 6\times ^3/_4$ cM. colour bluish red, Malpighian bodies not conspicuous, connective tissue seems increased. One accessory spleen. The connective tissue of the stem shows a bloody infiltration. The liver proved larger than one had thought during life, weight 110 g, on section a brownish colour, connective tissue increased, structure not clearly visible. No enlarged glands in abdomine.

Kidneys, somewhat larger than normal, pale in colour, capsule eaily loosened, on section colour brownish and the aspect somewhat gelatinous. The anatomical structure of the cortex is lost and in some spots the borderline between cortex and medulla cannot be seen. The aspect of the right and the left kidney agree, except that in the left one the connective tissue surrounding the capsule is infiltrated with blood.

The bone marrow is cherry red in colour.

Microscopical examination.

Liver. The parenchyma of the livercells is slightly vacuolized, the radiar structure of the organ is partly lost. The capillaries are moderately filled with blood. Kupfer's cells are not swollen. The capsule is slightly infiltrated with small round cells. In the liver a large number of infiltrations are seen in the portal canals, but also beyond (Fig. 7). Generally a connection of these spots with a bloodvessel is to be found (perivascular situation), but this is not invariably so. These foci are only partly localized in the capillary sinus as is the case in the embryonic blood-formations. They consist of uninuclear elements, partly resembling small lymphocytes, partly with more leptochromic nuclei and a broader protoplasmic border. Respecting these elements, there is certainly a pronounced resemblance with foci of blood formation, but normoblasts and more mature forms of red cells cannot be found, neither granulocytes. The latter are also lacking in the portal canals. There is a marked siderosis; blue pigment and diffuse

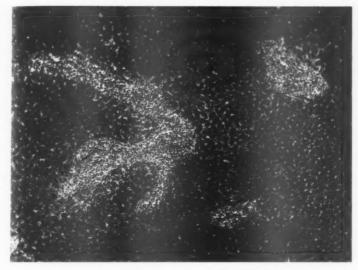


Fig. 7. Liver in the case of anemia e causa ignota.

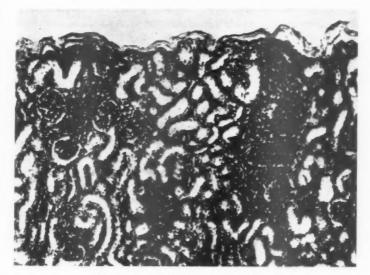


Fig. 8. Cell infiltrations in the kidney.

blue colouring of the liver cells, the adventitial layer of the blood-vessels and Kupfer's cells.

Spleen. Numerous Malpighian bodies showing no germinal centres, they are for the larger part sharply defined. Sinus somewhat narrow but sinus-endothelium not swollen. Slight siderosis of the reticulo-endothelium, the capsule and the trabeculae being free from iron. Pulpa hyperemic.

Kidneys. The glomeruli as a rule have a normal aspect, only very exceptionally containing a few cells or a single one in the capsule of Bowman. Some tubuli contain albumen. No siderosis. In the cortex infiltrations are seen with the aspect as described of the liver (Fig.8); here also a perivascular localisation is often clear.

Adrenals without anomalies.

Bone marrow. Smears and slides after embedding in paraffin, present a normal picture in which the granulocytes are amply represented.

Examination of the liver and the adrenals after Levaditi's method does not show any spirochetes.

Apex of the left lung: numerous alveoli contain edematous fluid, some ones loosened endothelial cells. The alveolar septa have thickened, there is peribronchitis, some bronchi are filled with exsudate.

Discussion.

What must the diagnosis be in this case, how was it possible that a breastfed infant of $2^{1/2}$ months could fall into this miserable condition, while the anamnesis supplied no clue? In our opinion congenital syphilis may be excluded because of the negative anamnesis, the negative reaction of Sachs-Georgi, the lack of perisplenitis, and spirochetes not being found in liver and adrenals. Congenital leukemia is of rare occurrence but reliable cases are described in medical literature. The microscopical investigation, however, refutes this diagnosis. Congenital anemia may be discussed, if we should be inclined to regard the cell infiltrations as foci of blood formation, though they differ from the

¹ e. g. Weston M. Kelsey Jr a Dorothy Anderson: A. J. D. Ch. 58, 1268, 1939, relate their own case and give a review of the literature.

latter by their localisation being mostly perivascular. Neither does the blood picture coincide here.

The contrast between the normal bone marrow and the picture of the circulating blood almost without granulocytes, is striking, but Lehndorff found in his cases of anemia allergica or temporaria also a wide difference, the bone marrow being active and the anemia aregenerative.

In the case mentioned above we dare not go beyond the diagnosis of anemia e causa ignota.

Anemia luetica.

Family C. Our next observation deals with the second child of healthy parents who emphatically deny a syphilitic infection. The first child was two months premature, had a distended abdomen, caught a cold (coryza?) and died soon afterwards.

The second child was born a month before term; she was breastfed. Three days before she was seen by one of us (J), the child was beginning to take her bottle badly and to groan. The groaning or whimpering increased. The child looked pale, the lips got sore. Shortly before the family physician had put a new dressing on the navel because of an hernia umbilicalis; at that time he was not struck by any marked distension of the abdomen. The following status was taken in visiting the child at her home: infant three weeks old, very ill, groaning continually, handling the child causes pain. Lips coloured brown from the application of tannin-glycerine. There are lipfissures, but they do not reach further than the lips. Conjunctivitis on the right eye. Abdomen markedly distended, veins showing and skin glossy. The tension of the abdomen is so pronounced, that it renders the palpation of the abdominal organs impossible. Palpation seems to cause pain to the child. On percussion dullness is stated. The umbilicus is closed, the scar being somewhat discoloured. No pus appears on stroking from the symphysis to the navel. Heart and lungs normal.

In the evening of the same day the writers visit the child together. The tension of the abdomen is now much less, a very large liver can be felt, also the spleen proves to be enlarged, but not in the same measure as the liver. The fontanel bulges slightly and the sutures have widened a little. There is no exanthema of the skin, no anal fissures and the lipfissures do not extend beyond the red of the lips. Edema of the thighs and the lower part of the back. The diagnosis of lues is discussed, but thought improbable, also because of the parent's pertinent negation. On the same day a ray picture was taken showing the enlarged liver and spleen and underneath the air containing intestines. The stools are normal, the child does not vomit, but still groans continually. Blood: hemoglobin 45 %, red cells 2 280 000, white 18 200. Differential: immature cells 9, metamyelocytes 3, bandforms 11, polynuclear 42, lymphocytes 27, transitionals 8 %.

Bloodsugar 74 mg-%.

No definite diagnosis can be made; several possibilities are discussed, inter alia congenital tumour of the liver (hemangioma-endothelioma).

On the following morning fresh blood escapes from the mouth and also a brownish vomit. Edema of the back, not of the legs. The tension of the abdomen is very pronounced. A bloodbulla, the size of a farthing, is developing on the left buttock. The patient takes her food badly.

Now 10 cc of the father's citrated blood is injected intramuscularly into the right buttock. A blood examination performed shortly after this yields a bleeding time of $2^{\prime}15^{\prime\prime}$, a coagulation time of 7^{\prime} , the platelets numbering 36 480. The urine is without albumen, but contains reducing substances, estimated at \pm 1 %. The quantity of urine does not suffice for an investigation as to the nature of the reducing substances. The sediment reveals urates.

Next morning at $8^{1}/_{4}$ the child dies. The parents themselves are anxious for a post mortem, which is performed at $13^{1}/_{2}$ by Dr. E. F. J. H. FALGER.

Post mortem. Corpse of a slightly interior infant, moderate rigor mortis, some purplish blue spots in the skin of the back. Marked tension of the abdomen, the umbilicus prominent. On the left buttock a small bulla containing brownish fluid. The

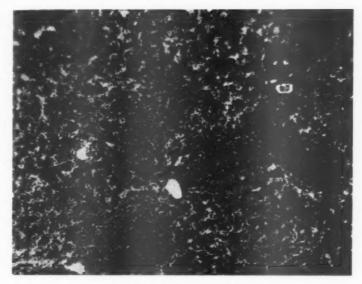


Fig. 9. Liver in anemia luetica.

subcutaneous tissues prove to be slightly edematous and the blood issuing looks watery. The liver reaches to three fingerbreadths below the costal margin and fills up half of the abdomen, the spleen does not reach the costal margin. All visceral organs have a pale aspect. The heart and the large vessels look normal with the exception of the right ventricle which is somewhat flabby and the foramen ovale being still open. Lungs without anomalies. The peritoneum smooth and shining, the intestines normal, the abdominal cavity without fluid. Weight of the spleen 34 g, a perisplenitis is lacking. Weight of the liver 297 g, on section the structure is not clearly discernible. The picture is not that of the flint liver. The colour is orange-yellow with numerous white spots (in formaline this colour disappears and is followed by a greenish tinge). Weight of the right kidney 15 g, of the left 14, of each adrenal 3. Weight of the brain 381 g. There is no macroscopic meningitis.

For further examination the organs are sent to the Laboratory of the Hospital for sick Children in Amsterdam.

The configuration of the braincortex proves normal. Cutting the brain into vertico-frontal slices in this case also reveals a dilatatio cavi septi pellucidi. On section the brain looks very pale. If this cerebrum be compared with that of a normal child, the impression is obtained, that in the former a slight degree of brainswelling is present.

Microscopical examination.

The *meninges* contain too many cells and in some spots the vessels are surrounded by cell cuffs.

Liver. In general the radial placing of the liver cells is fairly preserved but it is broken up by a large number of cell clumps which prove themselves to be miliar gummata. Some of them have a necrotic centre. They do not contain any erythroblasts nor elements of the myeloïd series (staining for blood cells after DOMINICI). The liver also contains a moderate number of foci of blood formation consisting of small round cells with dark nuclei, which can be clearly distinguished from the former. The liver parenchyma is not vacuolized, the cells do not contain any bile pigment, there are no bile thrombi. The bloodvessels, especially the veins, have thick walls with an infiltration of the adventitial layer. This is most marked in the venae sublobulares (Fig. 10). In the portal canals the vessels and bile-ducts have infiltrated walls. The intra-lobular connective tissue has slightly increased (Mallory's stain). In different places Kupfer's cells are swollen. There is only a slight siderosis and this is restricted to a number of Kupfer's cells and some adventitial layers which exhibit a faint blue tinge.

The liver is overcrowded with spirochetes (method of LE-VADITI). 0

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Spleen. The pulpa is hyperemic, the Malpighian bodies are for the greater part not sharply defined. The bloodsinus are narrow,

¹ In voce »Dilatatio cavi septi pellucidi» c. f. i, a. C. de Lange: Ned. Tydschr. v. Geneeskunde 86, 2507, 1942.

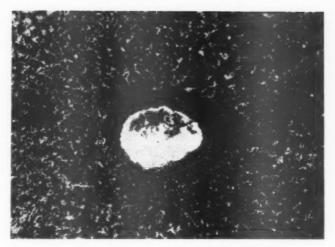


Fig. 10. Vena sublobularis with large sized cuff.

yet the endothelium of the sinus is not markedly swollen. The bloodvessels have fairly thick walls. The trabecular tissue looks normal. Also on microscopical investigation a perisplenitis is entirely lacking. The siderosis of the spleen is slight to moderate.

Kidneys. No anomalies. Siderosis lacking. The neogene zone still clearly apparent.

Adrenals. The blood-lacunae which at this age the adrenals normally present as a remnant of the primary reticular layer, are for the greater part absent in our case. The adrenals also are overcrowded with spirochetes.

Discussion. Small doubt can be entertained that in the child C the anemia was of syphilitic origin, yet there were several factors which led us astray: the pertinent negation of any infection of the parents, the acute beginning of the illness according to the anamnesis, the fissures limited to the red of the lips, the absence of an exanthema and of anal fissures and the liver, at least during life, with a much more impressive enlargement than the spleen, and after death no flint-liver and no perisplenitis. It is well

known, however, that of late the visceral symptoms in lues congenita often predominate over the skin manifestations.

After the microscopical investigation Wassermann's reaction was performed and proved positive in both parents.

Nephrogenic Anemia.

Our last case aroused clinically and also macroscopically at the post mortem a strong suspicion of lues congenita. In contrast to the foregoing observation, however, the microscopical examination proved this diagnosis to be wrong. We have headed it under the title of nephrogenic anemia, but are firmly convinced that this is a hypothesis and not a certainty.

Family D. The child Anton, second child of healthy parents is born spontaneous and à terme. Birthweight 4 250 g. He has been breastfed for a period of 6 weeks, after that he had allaitement mixte and at five months greens and potato-purée were given. When admitted to the hospital, his age was 6 months. According to the mother the child was born with a »tracheal obstruction». There had been a stridor from the beginning, but of late it had become much less apparent. The stools are normal, there is a slight cough and occasionally the child vomits. Since 3 weeks the patient is markedly pale.

The first child of the parents was a premature, who died at the age of 4 weeks and who had presented non descript cutaneous manifestations.

Status of Anton at the admission to the Emma-Hospital.

Pale child, does not present any skin manifestations with the exception of a slight dermatitis seborrhoïdes. Micropoly-adenia. Slight inspiratory stridor. Root of the nose somewhat sunken. Nihil in corde et pulmonibus. Abdomen much distended, umbilical hernia. Liver enlarged in a minor degree, surface irregular, deep incisure in the border. Spleen reaches two fingerbreadths below the costal margin. No particulars on neurological examination.

During the next days the following data are obtained. Reactions of Wassermann, Sachs-Georgi, v. Pirquet, Mantoux negative. Urine: albumen and urobilin positive, sugar negative,

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sediment many erythrocytes, some leucocytes and some granular casts. The urine examination was twice repeated, every time much albumen was found and the number of casts proved greater than on the first occasion.

Blood: hypochromic anemia, hemoglobin SAHLI 35 %, red cells 3 100 000, white 16 000. Differential: eos 1, bandforms 7, polynuclears 29, lymphocytes 63 %. Pronounced polychromia, poikilo- and anisocytosis, some normoblasts, no megaloblasts. Five days later on the differential formula revealed: baso 1, bandforms 7, polynuclears 21, lymphocytes 67, monocytes 4 %, polychromia etc as related above. On admittance and during the first days of the stay in hospital the child ran a temperature (a febris continua remittens) then the temperature sank to the level, but after two days pneumonia developed with a high febris remittens. The child was very ill and lost two kg in weight in a few days. Clinically a massive pneumonia of the right lower lobe was stated but also the left lung was attacked (X-ray picture) and diffuse râles were heard. On the X-ray picture the trachea proved visible over its whole course and seemed normal. Influenced by the pneumonia the percentage of the polynuclears rose to 54 %, the hemoglobintax being still 35 %. During the last days before death liver and spleen seemed to have diminished in size.

The child dies after a stay in the hospital of three weeks. Post mortem by Dr. J. C. Schippers, 13 hours after death. The right lobe of the *liver* is free from the diaphragm, on the left there is a perihepatitis. The convexity of the liver shows a reddish colour, which changes to yellow if one nears the lower border which is fairly massive. On the surface yellow spots,

somewhat sunken, present themselves, the same are seen on section, especially near the periphery. They resemble miliar gum-

mata. The liver's weight is 255 g (± normal).

Spleen weight 24 g (normal weight \pm 10 g), there is one accessory spleen, perisplenitis, on section only sparse follicles are visible. Intestines shining, coecum with appendix lying free in the pelvis minor.

Behind the manubrium sterni and also along the insertion of the diaphragm large lymphoglandulae are found.

⁷⁻⁴⁶⁸⁸⁵ Acta pædiatrica. Vol. XXXIV

Weight of the heart 45 g, heartmuscle somewhat pale, valves intact.

Lungs. On the lower lobe of the right lung near the diaphragm a pleuritis fibrinosa is found, the whole lower lobe shows a massive infiltration. In the middle and also in the upper lobe edema is present in several places and also small foci of bronchopneumonia. The middle lobe has been incompletely formed. On the anterior surface of the lower lobe on the right a small growth is seen. The left lung contains several foci of bronchopneumonia especially paravertebral; there also is bronchitis and some edema.

Microscopical investigation.

Liver, the capsule has thickened over the yellow spots, they prove to be formed by hyalinisized connective tissue which in-

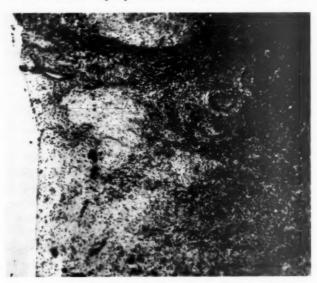


Fig. 11. Liver with hyalinisized connective tissue and septa of small round cells. On the right three obliterated bloodvessels. On the left and on the same level in the middle isolated bile ducts. At the bottom on the left isolated liver cells.



Fig. 12. Spleen with excessive thickening of the capsule.

cludes septa of small round cells. Here and there amidst the connective tissue some isolated liver cells and bile ducts are visible (Fig. 11). In the neighbourhood of the foci the connective tissue of the portal canals also has increased and there is a slight infiltration with round cells. The connective tissue in those portal canals shows a slight hyalinisation. The left lobe beyond the foci proves normal, apart from a slight fatty degeneration of the parenchyma and some minor infiltrations with round cells. The same holds good for the whole right lobe. The microscopical picture does not resemble that of lues congenita. No spirochetes

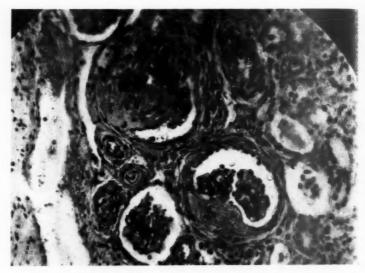


Fig. 13. Kidney with total and partial hyalinisation of glomeruli.

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are found after Levaditi's method. There is no siderosis to speak of.

Spleen, the Malpighian bodies are over the whole not conspicuous, most of them present germinal centres. There is a massive thickening of the capsule over the greater part of the spleen. In some places the capsule and the underlying layer of connective tissue can be seen as separated from one another, but elsewhere they form one massive layer (Fig. 12). The connective tissue is poor in fibers and cells and on staining for iron it proves to contain blue pigment in fairly coarse particles. Otherwise there is no siderosis. In the pulpa a moderate number of normoblasts is found and some clumps of immature cells, perhaps lymphoblasts, present themselves.

Kidneys, many tubules contain coagulated albumen, here and there intermixed with cells; the major part of the glomeruli is diseased, showing partial or total hyalinisation. The tubular epithelium is fairly well preserved, but some tubuli have widened

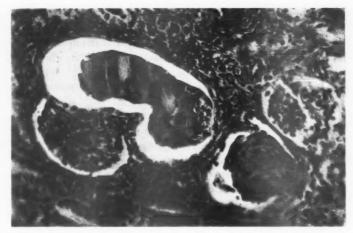


Fig. 14. Kidney: Widened tubule with albumen and cells, infiltration with round cells, hyalinisized glomerulus.

and their epithelium flattened. Here and there in the interstitium some infiltration with round cells is present (Fig. 13 a 14). There are many thick coated vessels.

This process is certainly not of recent date.

Right lung. The above described little growth beneath the pleura proves to be a lymph follicle richly vascularisized with a thin spreading into the interstitium of the lung and there again increasing in size.

Discussion. During life and also macroscopically at the post mortem there was a strong suspicion of lues congenita, which proved wrong. What was the cause of the anemia? Possibly the chronic nephritis, which may have led to a hypochromic anemia. The liver and the spleen proved almost normal, apart from the foci of connective tissue. Which process was at the bottom of the exuberant growth of connective tissue? This process is clearly not of recent date and the idea it being the result of an intra-uterine inflammation presents itself to our mind. The same process must have produced the chronic nephritis. Perhaps the enlargement of the lymphoglandulae behind the sternum and

along the insertion of the diaphragm also is a remnant of an old inflammation. Also the congenital stridor which lessened in the latter months, may have been caused by an inflammation. Perhaps the trachea or larynx has widened a little as the child grew older and so the stridor becoming less pronounced. We regret that here a microscopical investigation is lacking, the same holds good for the bone marrow.

Summary. The authors relate four cases of congenital (in a strict sense) anemia, the children being anemic at birth. Two of these are observations of their own, one with post mortem and microscopical investigation. The remaining two are quoted from the Dutch literature.

Then follows a case of severe anemia with post mortem and microscopical investigation in a young infant; the cause of the illness could not be found. The next case deals with an anemia luetica. This diagnosis had been discussed during life, but thought improbable. Miliar gummata in the liver and numerous spirochetes in liver and adrenals, however, did not leave any doubt as to the origin of this anemia.

Finally they relate a case they have called nephrogenic anemia, the kidneys showing a hyalinisation of the major part of the glomeruli and the liver and the spleen presenting an exuberant growth of connective tissue. The authors are inclined to the hypothesis that an inflammatory process may be held responsible for these alterations and the resulting anemia.

Haemosiderosis pulmonum.

By

PER HANSSEN.

Haemosiderosis pulmonum, which is almost exclusively confined to childhood, was till a few years ago regarded only as a pathological-anatomical curiosity. But, since the publication of a certain number of cases, it has become possible to make a clinical diagnosis, and in a few cases the diagnosis has been made »intra vitam» by Waldenström and probably also by Nitschke.

The reason for publishing a short account of the following case (after Gellerstedt-Waldenström and Selander in Sweden have given a detailed description of this disease) is that we were able to recognize this condition clinically, and have confirmed the diagnosis by the demonstration of »heart failure cells» in sections prepared from the blood-stained sputum.

The patient was 6 years old when the disease began in the spring of 1939, and she was $10^{-1}/_{2}$ years old when she died in August 1943 after the disease had lasted fully four years. While under observation she was admitted to hospital on five occasions, thrice to the Fever Department, and twice to the Medical Department. One of her hospital periods lasted ten months, two lasted three months each, and one lasted two months, so we were able to follow the development of the disease. As haemosiderosis pulmonum was not diagnosed clinically till a time between the fourth and fifth hospital periods, the examination during the first periods was not as comprehensive as desirable.

The event which led to her first admission to hospital was a series of haemoptyses which recurred throughout her disease at shorter or longer intervals, overtaking her every day during the worst periods. It was curious that the haemoptyses were almost exclusively confined to the morning hours, being rare later on in the day except for the periods with pneumonia complications. The blood was always intimately mixed with mucus, forming round lumps of sputum which were hawked up. On most mornings one or a few lumps appeared. The sputum was never seen to be streaked with blood, and there were no freshly frothing haemoptyses.

During her periods in hospital, she hardly coughed at all apart from this hawking up of sputum in the morning.

At first pulmonary tuberculosis was diagnosed, and the x-rays, which showed extensive lung infiltrations, seemed to confirm this diagnosis which we considered could be excluded because of the course of the disease, the repeatedly negative tuberculin tests and the repeated failure to cultivate tubercle bacilli from the sputum. During the two first periods in hospital, between May and June and between August and October 1939, there was a moderate degree of anaemia (60—70 per cent haemoglobin) and a normal E. S. R. She was given iron, and the percentage of haemoglobin rose somewhat.

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Between October and December 1939, her condition deteriorated considerably and her anaemia increased. On admission to hospital in December 1939, the percentage of haemoglobin was only 30.

During the first part of this hospital period there was a rapid rise of the haemoglobin figures, but this rise may have been due to a blood transfusion and the administration of liver extract or iron. When she was given no iron during one period, the haemoglobin percentage fell rapidly, rising again when the administration of iron was resumed. The same observation was made on a later occasion. During her second hospital period, the percentage of haemoglobin remained comparatively constant under treatment with iron. This was also the case after this hospital period, even at the times when she received no iron. Her response to iron suggests that she was suffering from sideropenic anaemia. Unfortunately the serum-iron was determined

on only one occasion (November 1942) when it was found to be comparatively high, $83~\gamma$ per 100 ml blood. But at this time the patient was not anaemic.

While she was anaemic, her anaemia was definitely hypochrome, but it became orthochrome after treatment with iron.

During her various hospital periods, the leucoeytes ranged between 5 500 and 12 000, on many occasions with an eosino-philia of 6—8 per cent. There was also constant reticulocytosis, from 10 % to 100 %, pathological urobilinuria, serum colour between 5 and 12 (Meulengracht's method), and the osmotic resistance of the erythrocytes was normal. On two occasions an Ewald test meal showed free hydrochloric acid in the stomach. There was no clinical or haematological sign of haemorrhagic diathesis. On two occasions sternal puncture showed no definite departure from the normal, notably no increase in the number of the erythroblasts in relation to the leucoblasts. E. S. R. usually between 10 and 20, the highest figure being 30. Thrombocyte counts on two occasions gave high figures, 340 000 and 505 000 with Thomsen's technique. Serological tests for syphilis were negative for both mother and child.

After she had been ill for about a year-and-a-half, she began to suffer from considerable dyspnoea with cyanosis of the lips on exertion. This condition was progressive and was most prominent when she contracted febrile infections of the respiratory tract. After the disease had lasted two years, she could no longer play with other children on account of her dyspnoea.

During the periods in hospital, there was no oedema, no albuminuria or enlargement of the liver and spleen. There was also no sign of valvular disease of the heart and no radiologically demonstrable enlargement of the heart. An electrocardiogram was normal except for right axis deviation.

In 1942 her fingers showed typical clubbing, with curved nails. The same changes were observed in the toes.

In the course of her illness, 15 radiograms were taken of her lungs. The first radiogram ($^{12}/_5$ 1939) taken immediately after the first haemoptyses, showed numerous ill-defined infiltrations in both pulmonary fields, being most numerous in the basal

areas. The size of these infiltrations varied greatly. The next skiagram, taken only ten days later ($^{22}/_5$ 1939) showed that the infiltrations had disappeared without leaving any definite parenchyma densities behind. It would therefore seem that the infiltrations revealed by the first skiagram had been induced by atelectases, — a quite common sequel to pulmonary haemorrhages. The next skiagram, taken when the percentage of haemoglobin was at its lowest ($^3/_1$ 1940), showed diffuse, dust-like infiltrations in both pulmonary fields. The vascular shadows in the hilus were not abnormally large, and there were no radiologically demonstrable changes in the heart.

All the skiagrams taken subsequently of the lungs showed the same very small, diffuse infiltrations in both pulmonary fields.

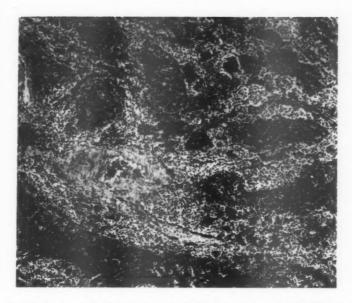
A radiological examination of the hands and feet showed none of the changes associated with BOECK's sarcoid.

After examining these skiagrams, T. Dale, M. D., Professor of Radiology, has expressed the opinion that, in his experience, such a radiological picture is confined to a few rare forms of pulmonary silicosis.

In 1940, her tonsils and adenoids were removed, and they showed lymphoid hyperplasia under the microscope. In December 1942, a small gland in the neck was excised for microscopic examination. (Throughout her hospital career the patient suffered from slight, general enlargement of the lymphatic glands.)

The account given of the microscopic examination by ERIK WAALER, M. D. is as follows: "There is lymphoid tissue with a considerable reticulum-cell reaction. The arrangement of the reticulum-cells is irregular, there are only a few nodules, and they are smaller than those commonly found in Boeck's sarcoid. No giant cells are visible in any of the nodules, and special staining has failed to reveal iron in the sections. The picture is suggestive of, but not characteristic of, Boeck's sarcoid.

In a section from the sternal marrow there was no demonstrable increase of the reticulum cells. In a section of a blood-stained lump of sputum, numerous lymphocytes, granulocytes and desquamated epithelial cells and masses of homogeneous



Microphoto 1. \times 100. Section of excised gland showing a considerable reticulum cell reaction. The reticulum cells are arranged in irregular strands and heaps.

mucus were found. There were also large cells with a large amount of cytoplasm and round to oval nuclei, the cells being completely filled by coarsely granular pigment. This pigment, which was also to a certain extent extra-cellular, gave a strong iron reaction.

During the last half year of the patient's life, the clinical picture was dominated by increasing dyspnoea and cyanosis which were worst when the patient contracted febrile infections of the respiratory tract. There was no anaemia during this last half year.

Owing to the war, the patient spent the last months of her life far from Bergen, and a post-mortem examination was not made. Her death was due, as far as I can make out, to her pulmonary condition and the dyspnoea accompanying it.



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Microphoto 2. × 600. Section from a blood-stained lump of sputum. In addition to lymphocytes, granulocytes and mucus, there are some large cells completely filled by a coarsely granular pigment giving a strong iron reaction.

Although a pathological-anatomical confirmation of the diagnosis is lacking, I believe that the combination of the signs — sideropenic and haemolytic anaemia, recurrent haemoptyses and miliary infiltrations of the lungs in a young female — is sufficient to justify as highly probable the diagnosis of haemosiderosis pulmonum. The demonstration of »heart failure cells» in the sputum of a patient showing no other sign of heart disease, clinches this diagnosis.

As far as I can see, about 15 cases of this disease have hitherto been published (Anspach, Borsos-Nachtnebel — 3 cases — Ceelen — 2 cases — Glanzmann and Walthard, Montaldo, Nitschke — 2 cases — Pilcher and Eitzen, Reye, Selander, Waldenström and Gellerstedt — 2 cases, — and »some cases» referred to by Virchow).

Our case is illustrative of the characteristic intermittent

course of the disease and of the behaviour of the anaemia which even though it may be severe (haemoglobin 30 per cent) at one stage of the disease, need not necessarily continue to be so later on; and death may occur without the patient being anaemic. The iron requirements evidently vary in the different phases of the disease.

The particular type of anaemia, - a mixture of sideropenic and haemolytic anaemia — which WALDENSTRÖM has described in such detail and which existed in our case, goes far to support the diagnosis which is suggested by the characteristic radiological changes. In Acta Radiologica, Waldenström has recently discussed the differential diagnosis in detail from the radiologist's point of view, and I would refer readers to his account of the changes in the lungs. As already pointed out, the histological examination of a gland taken from the supraclavicular fossa showed so great a reticulum cell reaction that the diagnosis of Boeck's sarcoid had to be considered. Waldenström found a similar condition in an excised gland in one of his cases, but his post-mortem examinations of the other organs have yielded no supplementary evidence in support of this diagnosis. At several post-mortem examinations (Montaldo, Selander, Wal-DENSTRÖM and GELLERSTEDT, GLANZMANN and WALTHARD, Reye) a considerable reticulum cell reaction has been observed in the bronchial and in a few cervical glands. But in all these cases there were at the same time also found definite to considerable haemosiderin deposits in the same gland and often at the same time giant cells containing several nuclei. The reticulum cell reaction in these glands must therefore be interpreted as a sequel to haemosiderin deposits.

Our case shows that the same reticulum cell reaction can be observed in glands in which haemosiderin, demonstrable by ordinary histological methods, has not yet been deposited. For in view of the available post-mortem findings we must assume that the broncial glands also in our case contained haemosiderin.

Our patient presented clubbed fingers and curved nails during the latter part of her life. As the patients observed by Selander and by Pilcher and Eitzen presented the same condition, it is probable that clubbed fingers and curved nails are a not infrequent sign of this disease of the lungs which is associated with evanosis.

WALDENSTRÖM remarks that the demonstration of »heart failure cells» in blood-stained sputum is instructive, but he failed to find them in the case in which he had occasion to look for them. Our case is presumably the first in which they have been found.

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Several earlier authors have evolved theories to explain the pathogenesis of this disease, but as far as one can judge, none of them is very convincing.

In 1944, HEILMEYER advanced a new — and presumably better — theory, comparing haemosiderosis pulmonum with haemochromatosis. Hence his suggestion that the deposit of iron in the lungs is the primary factor in the disease, the sideropenic anaemia being secondary in relation to the deposit of iron. But Heilmeyer does not know why this enormous deposit of iron in the lungs takes place.

Summary.

A case of haemosiderosis pulmonum is recorded in a girl who was $6^{1}/_{2}$ years old when the disease began and $10^{1}/_{2}$ years old when she died. The diagnosis, made during life, depended on the signs: An intermittent course of the disease, sideropenic and haemolytic anaemia, numerous haemoptyses, miliary infiltrations of the lungs and sheart failure cells in a section of the blood-stained sputum. There was no sign of heart disease. No post-mortem examination.

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Two Cases of Hermaphroditismus Femininus.

By

IVAR NORDAHL.

By a hermaphrodite we mean an individual who has both sexual gonads — testes and ovaries — and the genital organs of both sexes and who is capable of functioning both as a man and as a woman. Such individuals have doubtless never existed. In the lower animal kingdom, however, such creatures are to be found — and higher up in the scale of development, for instance in the eel, sex constitutes a function of age, the animals being male when they are young and female when they are old.

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In man it has been sought on purely anatomical basis to divide the hermaphrodites into two main groups: hermaphroditismus verus, where the gonads of both sexes are present, and pseudoaphroditismus, where only ovaries or testes are existent, but where the malformation of the external genitals renders the determination of sex uncertain. This classification gives us no guidance as to the cause of the malformation and it has therefore, generally speaking, been abandoned.

Goldschmidt's doctrine of intersexuality is based upon experiments with some species of butterflies and it is the effect that under certain conditions there may develop individuals who are neither male nor female, but a kind of intersex. Diefenbach, however, has reported the occurrence of 8 cases of pseudohermaphroditism through 5 generations, that is to say, a hereditary foundation for hermaphroditism. The condition which will here be discussed — hermaphroditismus femininus — has, however, its definite cause, namely, hyperplasia or tumour-

formation in the suprarenal glands, wherefore the anomaly may best be designated suprarenal pseudoaphroditism, or suprarenal fetal virilisation.

In this condition, which was first described by Fiebiger in the beginning of the present century, we find:

- 1. Greatly enlarged suprarenals.
- 2. Hypoplastic or infantile ovaries.
- 3. Enlargement of the clitoris.
- 4. Persistence of the sinus urogenitalis.
- 5. Prostata.

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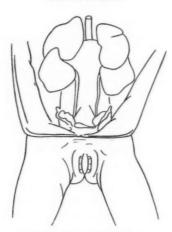
It is due to hyperfunction of the suprarenal cortex.

There is a great difference in the suprarenals before and after birth. In fetal life they consist exclusively of cortex and in relation to the size of the organism the proportion of cortex is from 30 to 50 times greater. This ratio becomes altered immediately after birth, as the cortex rapidly atrophies and the suprarenal medulla develops. According to Brock the suprarenals weigh up to the 1st month 3.91 g, from the 2nd to the 12th month 2.85 g. In a fetus with a length of 10 cm the kidneys and the suprarenals are equally large. In newborn infants the ratio of weight between kidney and suprarenal gland is 1: 3. In adults it is 1: 20. The change in the suprarenals is reckoned to have been concluded at the age of 1 year. The ratio between the mesodermal cortex and the ectodermal medulla has then become permanent.

In case of pseudohermaphroditism the fetal conditions in the suprarenals persist in some degree. It is not the whole of the cortex that determines the virilisation, but a zone of androgenic cells which lies on the inner side of the cortex and which normally disappears after birth. This androgenic zone is not found in all forms of animal life. According to Yasukawa it occurs only in man and probably in anthropoid apes. It is this persistence of the androgenic zone that leads to masculinisation in individuals of feminine constitution.

In the adult woman we know that tumours in the suprarenal glands, in the ovaries (arrhenoblastomata), in the hypophysis and in the thymus may have a virilizing effect, such as may be

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Diagrammatic presentation.

seen in Cushing's disease in women, in Achard & Thiers disease (Diabète des femmes à barbes» — Diabetes in bearded women) and in Stewart-Morel's syndrome (osteoporosis, hypertrichosis, virilism, obesity and osteophyte-formation on the inner side of the os frontis). Here the suprarenals undergo no change. This they do, however, in case of the virilism occurring at the climacterium, where they are enlarged. Tumours of the suprarenal cortex arising before puberty give the picture of a pubertas præcox, with marked growth of the clitoris in girls. In case of virilizing tumours in the suprarenal cortex a considerable excretion of androgenic and oestrogenic hormones in the urine has been noted. It was formerly supposed that these hormones originated from the testes and ovaries, but it is probable that they can be produced in the suprarenal glands.

To diagnose the malformation is perhaps fairly easy, but the diagnosis of the cause presents great difficulty, and it may be very difficult, if not impossible, to decide whether there exists a masculine or a feminine pseudohermaphroditism. As regards the therapeutic treatment, which is most often surgical, it is advisable to wait as long as the sexual life remains infantile, un-

less we have made sure that the cause lies in the suprarenals, in which case resection is indicated.

The two cases of feminine pseudoaphroditism which shall here be described must be regarded as unique, firstly because in the illes of the Dept. no record of this diagnosis is to be found during the last ten years, and secondly because we have here two nearly dentical cases, in patients of almost the same age, who died within some few hours of each other.

The first patient, Jenny C., was six weeks old. No known cases of malformation in the family. Normal weight at birth. Length 51 cm. mmediately after birth it was found that the genitalia were abnormal, and the child was given the name Jenny, so that it could easily be changed to Jonny, if a mistake had been made respecting the sex. Already at birth the clitoris was very large. From the very first the child was very unwilling to take the breast, and even attempts at feeding with bottle and teat were unsuccesful. The child was constantly vomiting, but without signs of gushing, and the weight steadily decreased. When one month old the child weighed 1/2 kg less than at birth. No definite cause of the vomiting could be discovered. The defecation was somewhat costive. Urination normal. On admission the child was small and thin and weighed 2 350 g. Length 53 cm. General examination revealed nothing abnormal, apart from the external genitals: The clitoris was 2 cm long. Under this was seen a small vaginal orifice, and on probing this there was found a vagina of about 3 cm. From the clitoris two leaves lead over to the labia minora. The labia majora are well-developed, and there is seen an urethral orifice of normal appearance. The vomitings continued and the child's condition became steadily worse. It was shrivelled up, with raised folds of skin. Radiographic examination gave negative findings. A survey of the abdomen showed meteorism, but otherwise nothing abnormal. The condition grew worse and death supervened at 11 a.m. on April 2nd.

Laboratorial findings: Hb. 97 per cent. Erythrocytes: 4.7 million. Leucocytes: 11 600. R. R. 27 mm.

Prothrombin time: 27 sec. Urine: physiological.

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Autopsy revealed: Suprarenals: Left: 11 g. Usual appearance and consistence, without macroscopically visible tumours. Cortex yellowish, at the edge of the cut-surface deliquescent. Microscopical examination showed a very broad cortex and narrow medulla. Otherwise nothing to note.

The kidneys weighed 28 g (normal weight for the age). Suggestion of lobular division. Consistence as usual. The capsule is not quite easily detachable. The surface of the kidneys has a somewhat mottled appear-



ance, especially the right kidney, with more yellowish areas of varying size. On the cut-surface are seen slightly blurred markings and also here the same irregular yellowish areas. Otherwise the boundary between medulla and cortex is relatively sharply defined.

Vesica: Contains 20—30 cc of quite turbid urine. Mucous membrane distinctly injected.

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Genitalia interna: Ovaries and tubes of usual appearance and size, likewise the uterus.

Genitalia externa: The clitoris is considerably larger than usual and has a length of 2 cm. The præputium glandis continues over into somewhat hypoplastic labia minora, while the labia majora are of usual ap-

pearance and size. At the base of the clitoris on its under side is seen a small aperture with the appearance an orificium urethrae externum, but it is found that a probe can penetrate only 1 mm within the outer opening. Below this is found an aperture with the appearance of a vaginal orifice, hardly large enough to admit a pencil. On slitting up the posterior wall hereof it is seen that the mouth of the urethra lies 2 cm behind the base of the clitoris together with the vaginal orifice, so that the vagina and the urethra thus have for a distance of about 2 cm a common canal, which on macroscopical inspection seems to be lined by urethral mucous membrane. Nothing to note in the portio uteri. The uterine cavity can be probed. Microscopy revealed an interstitial nephritis. The ovaries showed numerous primordial follicles, as well as some few Graafian follicles. Otherwise nothing to note.

The anatomical diagnosis is: Feminine hermaphroditism, with greatly enlarged clitoris and large labia majora. Common canal for urethra and vagina. Hyperplasia of suprarenal glands. Cystitis and pyelitis. Interstitial nephritis. Emaciation and dehydration.

The second patient was Anne-Lise K., aged 7 weeks. Normal weight at birth. Frontal presentation. Delivery by forceps. Exclusively breast-fed. From the age of 3 weeks vomiting during and after meals. The vomiting came in spurts. Treated with eumydrin. Now and then the child has had twitches in head and legs. At the general examination on admission to the hospital nothing of note was found, apart from the genitalia: The clitoris is very large and lies as a penislike formation in the vulva. On the under side of the clitoris was seen an orifice the size of a pinhead, which could not be catheterized. Behind this was seen a slightly larger orifice which could be catherized by an ureteral catheter. This penetrated 1 $^{1}/_{2}$ cm and clear urine was drawn out. The labia majora were distinctly developed. While in the hospital the child had brief attacks of twitchings in arms and legs. The patient had frequent vomitings all the time, became worse and worse and died on April 3rd at 7 a.m. After death there came some bloody fluid from the mouth.

Autopsy. Genitalia externa: The clitoris is greatly enlarged, about 1 cm long and not quite so thick as a pencil. There is no distinctly visible glans or præputium. Just on the under side of the extreme point of the clitoris there is a suggestion of a minute aperture, which cannot be penetrated, even by the thinnest probe. Farther back there is somewhat larger opening, which can be probed for a distance of 3.5 cm upwards and backwards. The labia majora are distinctly developed. The labia minora cannot be detected with certainty. The skin on the labia



majora is possibly a little thick, and may perhaps be suggestive of scrotal skin.

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Suprarenals: The left gland weighs 9 g, the right 6 g. Both are distinctly enlarged, grayish-green in colour. Seen from the front, they cover about half of the kidneys. No tumour-formation in the suprarenals. The kidneys together weigh 27 g. Otherwise nothing to note. Renal pelvis and ureters: There are double ureters on the left side, opening separately into the bladder.

On slitting up the canal which could be probed from the vulva it is found that at a point about 1 cm upwards it divides into two parts, of which the anterior leads into the bladder, while the posterior part.

where the mucous membrane shows a wrinkled surface and has the appearance of vaginal mucous membrane, leads up to the portio about 2 cm above the point where the canal divides. While the outermost part of the canal and that which continues up to the bladder is very thin, the part leading up to the portio a good deal thicker, being about the width of an ordinary match. The uterus is about the size of a nut. Nothing special to note. The ovaries are of the usual appearance, presenting nothing specially noteworthy. No signs of testicles or prostata are to be found. Microscopy revealed ordinary ovarial stroma, with numerous primary follicles. There are also several Grafian follicles to be seen at the site of a cumulus oopherus. Nothing to remark about the tubes. Longitudinal section through genitalia interna: A common canal for vagina and urethra is seen to be lined by a multistratified squamous epithelium. A short distance inwards from the opening of the common canal into the vulva are seen, a little way under the epithelium, some gland-lumina, lined by a high-cylindrical epithelium and surrounded by unstriated muscle. Deeper down in the tissue, and still farther out towards the orifice of the canal, is seen a somewhat larger assemblage of gland-lumina. The lumina are arranged in small groups and clothed by a unistratified, cubic to cylindrical epithelium, with smooth surface in towards the lumen. Immediately around the gland-lumina is seen a multicellular connective tissue. Outside of this and between the groups of glands are found numerous strips of unstriated muscle. Higher up is seen the beginning of the vagina, lined by a regular, multistratified squamous epithelium, which on the portio merges into a cylindrical epithelium. The uterine cavity is lined by a low-cylindrical epithelium. Some few uterine glands are to be seen. Nothing to remark about the uterine muscles. Around the uterus are seen several sympathetic ganglia and nerve-fibres.

The suprarenal bodies show normal adrenal tissue, with the usual ratio between cortex and medullary substance.

In the other organs there was nothing to note, either on macroscopical or microscopical inspection.

Anatomical diagnosis: Pseudohermaphroditismus femininus. Enlarged clitoris and little developed labia minora. Common orifice for vagina and urethra. Hyperplasia of suprarenal glands. Double ureter on left side.

Summary.

Two cases of hermaphroditismus verus. The cases are almost congruent. The patients are, practically speaking, of the same age. Both have greatly enlarged clitoris, persistent sinus urogeni-

talis, hyperplasia of the suprarenals and malformation of the external genitals. As to the cause of death it is difficult to say anything definite. One of the patients had an infection of the urinary ducts, but can hardly be thought to have been lethal. In the other case no infection was noted. As to whether endocrine anomalies may have been the cause of death it is impossible to express any opinion.

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Über die Bluttransfusionen mit frischem und konserviertem Blut im Säuglingsalter.

Von

N. HALLMAN.

Ober den Einfluss des frischen Blutes und des konservierten Zitratblutes auf das rote Blutbild.

Die Bluttransfusionen sind in der letzten Zeit in der Therapie sowohl der Erwachsenen als auch der Kinder zu einem immer wichtigeren Faktor geworden. Bei den Säuglingen hat die Infusionsweise wegen der Kleinheit der Blutgefässe Schwierigkeiten bereitet, aber nachdem man darauf gekommen ist, zu diesem Zweck die oberflächlichen Venen des Kopfes zu benutzen, kann die Blutinfusion sogar mehrere Male pro Tag vorgenommen werden, ohne dem Patienten nennenswerte Beschwerden zu verursachen. Weiterhin sind die Infusionen sehr erleichtert worden durch die Ingebrauchnahme von konservierten Blut, wobei man nicht von der Anwesenheit des Blutspenders abhängig ist. Ausserordentlich vorteilhaft ist dies während des soeben abgeschlossenen Krieges gewesen.

Im allgemeinen ist man der Ansicht, dass das konservierte Blut dem ganz frischen Blut nicht ganz gleichwertig sei, obwohl es zahlreiche Anhänger hat und genügende Indikationen in gewissen Fällen und unter bestimmten Umständen.

Die Konservierung des Blutes wird ermöglicht durch seine Behandlung mit bestimmten Stoffen, welche die Gerinnung verhindern. Meistens wird zu diesem Zweck entweder Zitrat oder das auf andere Weise wirkende Heparin benutzt. In Finnland ist allgemein das Zitratblut im Gebrauch. Meistens haben die Bluttransfusionen den Zweck, eine aus irgendwelchen Gründen entstandene Anämie zu elimnieiren und gleichzeitig oft Flüssigkeitsverlust auszugleichen. Die Bestandteile des Blutes kann der Organismus des Empfängers natürlich auch auf andere Weise ausnutzen, entweder als solche oder durch Abbau zu geeigneter Form. Auf die Immuntransfusion ebensowenig wie auf andere Indikationen möchte ich in diesem Zusammenhang nicht eingehen.

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Wenigstens bei der Verabreichung von frischem Blut bleiben die infundierten Blutkörperchen im Organismus des Empfängers am Leben, natürlich unter der Voraussetzung, dass das verabreichte Blut zu einer in jeder Beziehung passenden Gruppe gehört. Diese Tatsache zeigen zahlreiche Untersuchungen über das Blutbild (z. B. Schaeffer bei Kindern), die Agglutination (Ashby, JERVELL u. a. m.), die Blutkompensation bei Versuchstieren (OTT, PANUM, EULENBERG und LANDOIS, KONRICH u. a. m.) und die Sauerstoffkapazität des Blutes (WILDEGANS, GOHR-BRANDT), sowie äusserst anschaulich die mit hyperchromischen Blutkörperchen (WILDEGANS) und Ovalozyten (VISCHER, SKÖLD, BUGENBERG, DE JONG) durchgeführten Blutinfusionen. Es gibt jedoch auch Forscher (Kuhl, Gladstone, Kunz und Zachel u. a. m.), welche zunächst auf Grund der bei der Obduktion nach Bluttransfusionen anzutreffenden Hämosiderose der Milz behaupten, dass die übertragenen Blutkörperchen regelmässig zugrunde gingen, und dass die im Blutbild usw. auftretenden Veränderungen ganz sekundärer Art seien.

Die klinischen Erfahrungen bei der Verabreichung von konserviertem Blut sind im allgemeinen und besonders während der Kriege günstig gewesen. Bei Versuchstieren konnte ²/₃ der Blutmenge kompensiert werden (Reissman und Heim). Konrich kommt mit Zitratblut nicht zu ebenso guten Ergebnissen, aber Breckenfeld gelang es nicht, seine Versuche zu wiederholen. Bezüglich der schweren Anämien und Blutverluste wissen wir andererseits, dass der Organismus nicht unbedingt einen sehr grossen Teil seiner Blutmenge zum Transport des Sauerstoffs benötigt, und andererseits sind wir imstande, auch mit Plasma und Serum sogar 80 % des Blutes bei Versuchstieren zu ersetzen (Levinson,

NEUWELT und NECHELES, MAGDALARY, SALANDT und BEST), was mit Zucker- und Salzlösungen nicht möglich ist (BUTTLE). -Bei der Konservierung verändert sich die Sauerstoffkapazität des Blutes, unabhängig von der Konservierungsmethode (Zitrat, Heparin), nicht nennenswert (OWADA, FISCHER und SCHURCH, MITTELSTRASS, HEIM). Bei der Verabreichung von konserviertem Heparinblut verhalten sich die Sauerstoffkapazitäten in ganz der gleichen Weise wie bei der Verabreichung von frischem Blut (REISSMAN und HEIM). Zahlreiche Versuche haben gezeigt (ME-TIS), dass der Transport des Sauerstoffs im Blutgefässsystem unbedingt an die roten Blutkörperchen gebunden ist, obwohl die Bindung des Sauerstoffs an das Hämoglobin ein rein chemischer Vorgang ist. Mit blossem Hämoglobin ebensowenig wie mit hämolysiertem Blut sind wir nicht imstande, erfolgreiche Blutinfusionen durchzuführen. Andererseits wissen wir, dass die roten Blutkörperchen leicht sogar dem Organismus fremdes Hämoglobin aufnehmen, und das Verhalten der Sauerstoffkapazität liesse sich auch auf diese Weise erklären.

Auf Grund von Agglutinations-Versuchen behaupten viele Forscher, dass bei der Verabreichung von Heparinblut 14 Tage lang konservierte rote Blutkörperchen im Blutgefässsystem des Empfängers fast ebenso lang leben wie auch die eigenen Blutkörperchen des Empfängers (u. a. Dekkers, Bushby und Whitby, MONTAGNE und PATERSON, MOLLISON, KRÜPE). BELK und BAR-NES dagegen behaupten in ihren bei Kindern durchgeführten, auf den M- und N-Eigenschaften basierenden Untersuchungen, dass die Zellen des konservierten Zitratblutes nicht am Leben bleiben, wenn die Konservierungszeit 2-3 Tage überschreitet, sondern dass sie verhältnismässig schnell nach der Infusion zugrunde gehen. Zum ganz gleichen Resultat sind Ross und Chapin, welche bei ihren Untersuchungen radioaktives Eisen zu Hilfe nahmen, später auch bei Erwachsenen gekommen. Trotzdem wirkt das Zitrat an sich nicht giftig. Es kann i. v. ganz gefahrlos in viel grösseren Mengen verabreicht werden, als zur Verhinderung der Gerinnung des Blutes jemals erforderlich ist (NEUHOF und HIRSCHFELD).

Da bei uns Finnland und somit auch in der Kinderklinik

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ständig konserviertes Zitratblut zur Verfügung steht, welches täglich zahlreichen Patienten verabreicht wird, dürfte es angebracht sein, seine Wirkung näher zu klären. Viele Autoren habet mit Hilfe von Volumenbestimmungen festgestellt, dass die Blutmenge nach der Infusion schnell ihren früheren Umfang erreicht. oder nur dem Volumen der Blutkörperchen entsprechend zunimm (HERLYN, SHIBLEY und LUNDY sowie bei Kindern BAKVIN ASTROV und RIVKIN). Indem wir einfach das rote Blutbild verfolgen, erhalten wir durch die Infusion einer genügenden Menge Blut zunächst einmal eine grundlegende Auffassung über das Schicksal der roten Blutkörperchen. Da man besonders bei schweren Durchfällen und Erbrechen der Säuglinge gezwungen ist, sogar täglich mehrere Male Blut- und Flüssigkeitsinfusionen vorzunehmen, und so praktisch genommen das Kind i. v. mit Hilfe von Transfusionen zu ernähren, ist die genauere Verfolgung auch der anderen Bestandteile des übertragenen Blutes am Platze.

Die Verfolgung des Blutbilds.

Das bei meinen Untersuchungen gebrauchte Zitratblut ist so hergestellt, dass dem Blut unmittelbar im Zusammenhang mit der Entnahme 10 % 2,5 %ige Zitratlösung zugesetzt wurde. Danach wurde das Blut in den Gummidichtungsflaschen des Blutdienstes bei 4° im Eisschrank aufbewahrt. Die Konservierungszeit betrug 0—15 Tage. Vor der Infusion wurde das Blut untersucht, und sofern es auch nur ein wenig hämolysiert war, regelmässig abgelehnt. — Das Blut wurde mit einer 10—20 ccm Spritze unter Zuhilfenahme eines Gummischlauchs in die oberflächlichen Venen des Kopfes infudiert. Vor der Übertragung wurde es bis auf höchstens 37° erwärmt. — Das zum Vergleich angewandte native Blut wurde mit Hilfe paraffinierter Spritzen vom Spender direkt auf den Empfänger übertragen.

Wie bekannt hat die Erfindung des AB0-Systems die Durchführung der Blutübertragungen eigentlich möglich gemacht. Das Blut der zur 0-Gruppe gehörenden sog. Allgemeinspender wird in der Hauptsache in den Blutzentralen gebraucht, wo Blut für den allgemeinen Gebrauch gesammelt wird, wobei die Kenntnis der Blutgruppe des Empfängers nicht unbedingt notwendig ist. Das in meiner Untersuchung benutzte konservierte Blut gehörte

regelmässig zu dieser Gruppe. — Wenn die Bluttransfusion misslingt, wird die Ursache hierfür meistens automatisch in der Blutgruppe gesucht. Heutzutage sind wir ja imstande, nicht weniger als 72 verschiedene Gruppen und Untergruppen zu unterscheiden. Wenn mehrere Blutübertragungen nacheinander vorgenommen werden, ist der Rh-Faktor zu berücksichtigen. Rh-negative Personen gibt es jedoch verhältnismässig wenig, nur ca. 15 % von allen Menschen, und ausserdem wird der Titer im allgemeinen gegen Rh-positive rote Blutkörperchen nicht sehr gross, weshalb die hämolytischen Reaktionen im allgemeinen gefahrlos sind (WIDSTRÖM, WILANDER und SWEDBERG). - Ausser von der Blutgruppe ist der Effekt der Bluttransfusion noch von individuellen Faktoren abhängig. Die Blutfülle des Gefässsystems, das hämolytische System, die Reaktionsfähigkeit des Knochenmarks, die Krankheit des Empfängers und vielleicht andere, noch unbekannte Faktoren können von Bedeutung sein (MERKE).

Um alle möglichen Faktoren auszuschliessen, habe ich bei meinen Untersuchungsobjekten die Bluttransfusion mit frischem und konserviertem Blut beim gleichen Patienten nacheinander vorgenommen. Der Rh-Faktor ist nicht untersucht worden, aber der gleiche Empfänger erhielt immer Blut von verschiedenen Spendern. Bei der Verabreichung von nativem Blut und frischem Zitratblut wurde ausser Blut der 0-Gruppe auch solches von der eigenen Gruppe des Empfängers gegeben.

Die verabreichte Blutmenge variierte von 9—22 ccm pro Körpergewichtkilogramm. Nach der Literatur ist diese Menge als ziemlich gross anzusehen. Manche Autoren haben doch empfohlen, bei Säuglingen sogar 40 ccm/kg zu verabreichen (Schäffer).

Die Versuchsobjekte sind zum grössten Teil Konvaleszenten nach verschiedenen Infektionskrankheiten gewesen. Sie wurden jedoch aus solchen gewählt, deren Hämoglobin lieber unter als über 60 Sahli betrug. Einer von den Patienten war behandelt worden mit der Diagnose Anaemia alimentaria (Hgb. 26 Sahli), einer litt an kongenitaler Lues (Hgb. 40 Sahli) und fünf hatten Frühgeburtsanämie.

Die Blutuntersuchung wurde unmittelbar vor der Bluttransfusion vorgenommen und dann in den folgenden Tagen je nach

den täglichen Schwankungen. Die neue Übertragung wurddurchgeführt, sobald im Blutbild keine nennenswerten Veränderungen mehr vor sich gingen. Dies war gewöhnlich nach Wochen der Fall, bisweilen etwas früher. In einigen Fällen zwander Zustand des Patienten dazu, die Transfusion schon nach einigen Tagen von neuem vorzunehmen.

Insgesamt sind 26 Säuglingen 65 Blutübertragungen gegebet worden, davon 13 mit nativem Blut, 13 mit Zitratblut sofort nach dessen Entnahme und die restlichen 39 mit konservierten Zitratblut.

Nach der Bluttransfusion trat in 7 Fällen im Verlauf einiger Stunden Fieber auf, das von 37,4—40,2° schwankte. In zwei von diesen Fällen trat ausserdem Hämolyse ein. Der eine Fallwurde behandelt mit der Diagnose Lues congenita, und diesen war 20 ccm/kg Blut verabreicht worden. Bei den Luetikern geschieht die Hämolyse bekanntlich leicht. Fünf Tage später rief natives Blut der 0-Gruppe im gleichen Verhältnis verabreicht jedoch keine Reaktion hervor. Der andere Fall, wo der Patient Hämolyse bekommen hatte, war Nachzustand einer Sepsis; er hatte 7 Tage aufbewahrtes Blut erhalten. Auch in diesem Fall rief das eine Woche später verabreichte frische Zitratblut keine Reaktion hervor.

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Bei der Durchsicht der Statistiken lässt sich feststellen, dass immer in einem bestimmten Prozentsatz die Reaktion erhalten wird, ganz gleichgültig, was für Blut angewandt wurde. Die Reaktionsfrequenz variiert bei den verschiedenen Forschern beträchtlich. Es ist behauptet worden, dass es möglich sei, durch genügend gründliche Sorge für die Reinheit sowohl der angewandten Infusionslösungen als auch der Apparatur die Reaktionen fast vollständig zu verhindern. (Genauere Zahlen Widström, Wilander und Swedberg). Bei der Verabreichung von konserviertem Blut sind die Möglichkeiten für dessen Infizierung natürlich immer grösser. Obwohl man also auf Grund der Reaktionen keine direkten Schlussfolgerungen über die Vorzüge der verschiedenen Blutsorten ziehen kann, so ist die Infektionsgefahr bei der Anwendung von konserviertem Blut immer ein beachtenswerter Faktor, der die Gebrauchsfähigkeit beeinflusst. (Die

Blutsorten, welche eine Reaktion ergeben hatten, brachten bei den bakteriologischen Untersuchungen kein einziges Mal positives Resultat.) Die verschiedenen Blutsorten ergaben Reaktionen wie folgt:

Natives	Blut.										*		0 %
Frisches	Zitra	tb	lu	t.									7,7 %
Konserv	iertes	Z	itr	a	tb	lu	ıt			۰		٠	17.1 %

Wenn man die Patienten, welche die Reaktion bekamen, noch näher betrachtet, fällt es auf, dass diejenigen mit dem höchsten Fieber regelmässig alle Frühgeburten sind, bei welchen sich schon die übliche Frühgeburtenanämie entwickelt hat. Ihr Alter variiert von 2-4 Monaten. Von 5 Frühgeborenen hatten nicht weniger als 3 bei 4 Infusionen reagiert. Zwischen dem Geburtsgewicht, dem Gewicht bei der Infusion, dem Alter und der Schwere der Anämie einerseits sowie der Frequenz und der Stärke der Anämie andererseits lässt sich keine deutliche Beziehung wahrnehmen. Wie bekannt, kann man den Säuglingen im allgemeinen ohne Gefahr bis zum Alter von 6 Monaten Blut von jeder beliebigen Gruppe geben, weil Agglutinine frühestens erst im Alter von 6 Monaten im Serum auftreten. Noch weniger liesse sich denken, dass sie bei Frühgeborenen vorhanden wären. Offensichtlich ist bei den Frühgeburten im allgemeinen in diesem Alter das ganze Blutsystem noch unentwickelt, worauf auch die Frühgeburtenanämie hinweist.

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Wir prüfen nun den Einfluss der Blutinfusion auf das rote Blutbild. Sowohl das Hämoglobin als auch die Anzahl der roten Blutkörperchen nehmen bei dem gleichen Individuum regelmässig dann mehr zu, wenn für die Infusion frisches Blut benutzt worden ist. Der Zusatz von Zitrat hat keinen Einfluss auf die Effektivität, welche deutlich schlechter wird, wenn die Konservierungszeit 3 Tage überschreitet. Das Ergebnis stimmt überein mit den Feststellungen der Amerikaner Belk und Barnes.

Der Blutstatus des Empfängers hat hier keine Bedeutung. Mit über 3 Tage konserviertem Zitratblut erzielt man ebenso schlechte Resultate, ob das Hgb des Empfängers nun näher bei 60 Sahli oder bei 26 Sahli war, wie im schwersten Fall des Materials. Am höchsten sind die Werte des Blutbildes fast regelmässig 24 Stunden nach der Infusion (Schäfer). Danach sinken die Werte, bis nach 7—8 Tagen ein neuer geringer Anstieg folgt. Dieser ist jedoch viel niedriger und tritt nicht ebenso regelmässig ein. Wahrscheinlich beruht dies auf der anreizenden Wirkungdes Blutes auf die Neubildung, auf welchen Umstand in diesem Zusammenhang jedoch nicht näher eingegangen werden soll Die typischen Veränderungen des roten Blutbildes sind ersichtlich aus dem in Tabelle 1 dargestellten Fall.

Tabelle 1.

Fall Nr. 19. J. K. Alter 1 Jahr. Gewicht 7,55 kg. Diagnosis: Osteo-myelitis chron. Fistula cost. I 1. sin. Blut verabreicht 15 cem pro Körpergewichtkilogramm.

Tag der Untersuchung			ge au itratb	fbewal lut (0)	Frisches Zitratblut (0)							
Unterstichung				Hgb.	E.	I.	L.	Hgb.	E.	I.	L.	
Vor	der	Inf	usion		58 73	3,18	1,14	13,4	61/76	3,10	1,22	4,6
17	l'ag n	ach	der l	nfusion	60/75	2,95	1,26	14,9	75,94	4,32	1,08	4,8
3 7	Гаде	30-	20-	30	57/71	3,30	1,07	9,1	75 94	3,64	1,29	6,5
7	39	39-	30	30	65/81	2,89	1,40	11,6	75 94	4,72	0,99	9,5
10	30	30	20	30	57/71	2,79	1,27	6,4	75,94	3,95	1,19	7,6
14	39	30	30	30	61/76	3,10	1,22	4,6	74/93	4,31	1.07	7.5

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Es ist klar, dass die Wirkung der Bluttransfusion bei den verschiedenen Patienten nicht gleich ist. Es können dabei viele Faktoren beteiligt sein, wie schon oben erwähnt wurde. Aus Tabelle 2 gehen die Schwankungen des Hämoglobins und der roten Blutkörperchen in den ersten 24 Stunden nach der Übertragung hervor, also dann, wenn die Werte des Blutbilds am höchsten sind, sowie am Ende der Observationszeit, wo im Blutbild wenigstens täglich keine Veränderungen mehr auftraten. Die Werte sind als verändert angegeben worden, wenn die Differenz die mit 5 % berechnete Fehlergrenze überschreitet.

Bei der Verabreichung von nativem Blut wurde das Blutbild mit Ausnahme eines Falles regelmässig besser nach der Übertragung, und es war am Ende der Observationszeit nur in zwei Fällen das gleiche wie vor der Bluttransfusion.

Tabelle 2.

		ag n bertr	Am Ende der Observation										
Art des Blutes		Gestie- gen		Unver- ändert		Gesun- ken		Gestie- gen		Unver- ändert		Gesun- ken	
	Hgb.	Er.	Hgb.	Er.	Hgb.	Er.	Hgb.	Er.	Hgb.	Er.	Hgb.	Er.	
Natives Blut	12	12	1	0	0	1	11	11	2	2	0	0	
Frisches Zitratblut	12	10	1	3	0	0	11	10	1	1	1	2	
1—3 Tage konserviertes Zitratblut	6	7	1	0	0	0	6	4	1	3	0	0	
4—8 Tage konserviertes Zitratblut	7	5	11	7	3	9	8	3	9	5	4	13	
9—14 Tage konserviertes Zitratblut	2	3	4	1	1	3	1	2	5	4	1	1	

Das frische Zitratblut hat die Situation fast ebenso regelmässig gebessert, aber das Hämoglobin war trotzdem in einem Falle von 13, und die Anzahl der roten Blutkörperchen entsprechend in 2 Fällen bei Abschluss der Observationszeit im Vergleich zu den ursprünglichen Werten herabgesetzt. Sehr günstig wirkte auch das 1—3 Tage konservierte Zitratblut. Die Anzahl der roten Blutkörperchen blieb jedoch in nicht weniger als 3 Fällen von 7 unverändert. Aber auch bei diesen war in den Tagen nach der Infusion ein deutlicher Anstieg wahrzunehmen. Möglicherweise hat die Konservierung des Blutes schon jetzt in gewissem Umfange die Lebenszeit der übertragenen Zellen beeinflusst.

Wenn die Konservierungszeit länger ist, wird das Resultat weiterhin schlechter. Nicht nur, dass das rote Blutbild nicht besser wird, es wird in verhältnismässig vielen Fällen sogar schlechter. So war die Anzahl der Erythrozyten am Ende der Observa-

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tionszeit in 13 Fällen von 21 geringer als vor der Blutinfusion, wenn das Blut 4—8 Tage aufbewahrt worden war. Unmittelbar nach der Infusion hatte ihre Anzahl entsprechend in 9 Fällen abgenommen. Die Anzahl der Zellen hatte anfangs in 5 Fällen zugenommen, aber am Ende der Observationszeit nur in 3. Das Hämoglobin zeigte nicht ganz so grosse negative Veränderungen. Sein Wert wuchs anfangs in 7 Fällen, und nach Abschluss der Observationszeit war er in 8 höher als ursprünglich. — Wenn die Konservierungszeit 8 Tage überschreitet, bleibt die Wirkung ungefähr gleich.

Wie schon oben erwähnt worden ist, waren die meisten Patienten Konvaleszenten nach Infektionskrankheiten. Obwohl sie erst beobachtet wurden, nachdem der Allgemeinzustand schon verhältnismässig gut war, liesse sich doch denken, dass ihr Blutbild vielleicht auch ohne Blutinfusion besser geworden wäre. Dies wäre zunächst in denjenigen Fällen denkbar, wo die Situation nach Übertragung von konserviertem Blut besser geworden war. Den verschiedenen Patienten wurde ohne irgendwelche Regelmässigkeit bald zuerst frisches und bald wieder konserviertes Blut gegeben. Die regelmässig bessere Wirkung des Ersteren kann also aller Wahrscheinlichkeit nach nicht auf vorübergehenden Umständen beruhen, sondern sie ist tatsächlich der Beschaffenheit des übertragenen Blutes zuzuschreiben.

Beiläufig sei erwähnt, dass die Gesamtanzahl der weissen Blutkörperchen in den verschiedenen Fällen relativ stark variierte. Im allgemeinen schien sie bei der Verabreichung von nativem Blut am wenigsten zu steigen. Je länger das Blut konserviert worden war, umso öfter und umso mehr wächst die Anzahl der Zellen sofort nach der Übertragung. Die Schwankungen waren jedoch verhältnismässig gross, und die Anzahl konnte in allen verschiedenen Gruppen am nächsten Tage auch abgenommen haben. Irgendwelche klare Schlussfolgerungen lassen sich schwer ziehen.

Auf Grund der obigen Resultate lässt sich sagen, dass das länger als 3 Tage aufbewahrte Zitratblut das rote Blutbild bei Säuglingen nicht günstig beeinflusst. Die infudierten roten Blutkörperchen werden offensichtlich verhältnismässig sehnell eliminiert, und der aus ihnen erhaltene Baustoff wird jedenfalls nicht in grösserem Umfange für entsprechende neue Zellen benutzt, wenigstens nicht im Verlauf der beiden ersten Wochen nach der Infusion. Das native Blut und das weniger als 3 Tage konservierte Zitratblut steigert regelmässig sowohl die Menge der roten Blutkörperchen als auch des Hämoglobins, und der Anstieg im Blutbild bleibt fast ausnahmslos mindestens 2 Wochen lang bestehen. Das Resultat stimmt überein mit den Ergebnissen, welche Belk und Barnes mit ihren Agglutinationsversuchen sowie Ross und Chapin mit radioaktivem Eisen erhalten haben. Die ersteren sind bei Kindern durchgeführt worden, die letzteren bei Erwachsenen.

Zusammenfassung: Es sind 65 Blutinfusionen bei 26 Säuglingen durchgeführt worden, wobei dem gleichen Individuum nacheinander Nativblut, frisches sowie konserviertes Zitratblut gegeben wurde. Die verabreichte Menge variierte zwischen 9—22 ccm/kg.

Bei dem gleichen Individuum ist der Anstieg des roten Blutbilds regelmässig deutlich besser gewesen nach der Verabreichung von nativem oder weniger als 3 Tage konserviertem Zitratblut als nach Verabreichung von länger konserviertem Zitratblut.

Das native Blut erzielte in 11 Fällen von 13 einen mindestens 2 Wochen andauernden Anstieg sowohl des Hämoglobins als auch der Anzahl der roten Blutkörperchen. In 2 Fällen gingen die Werte in der erwähnten Zeit auf das ursprüngliche Niveau zurück.

Mit frischen und weniger als 3 Tage konserviertem Zitratblut stieg die Anzahl der roten Blutkörperchen anfangs in 17 Fällen von 20 und blieb auf dieser Höhe in 14 Fällen. In 2 Fällen nahm sie im Verlauf dieser Zeit ab. Der Hämoglobinwert stieg entsprechend in 18 und 17 Fällen und nahm einmal ab.

4—15 Tage aufbewahrtes Zitratblut verursachte unmittelbare Zunahme der Anzahl der roten Blutkörperchen in 8 von 28 Fällen, und dieser Anstieg blieb in 5 Fällen 2 Wochen lang bestehen. Die entsprechenden Zahlen des Hämoglobins sind 9 und 9. Die Blutinfusion rief Abnahme der Anzahl der roten Blut-

körperchen unmittelbar in 12 und später in 14 Fällen hervor, sowie Sinken des Hämoglobins entsprechend in 4 und 5 Fällen.

Von denjenigen Patienten, welche konserviertes Zitratbluerhalten hatten, reagierten 6 oder 17,7 % mit Fieber, und bei zwei von diesen trat Hämolyse ein. Von den Ersteren litten 4 an Frühgeburtenanämie. — Von denjenigen Patienten, welche frisches Zitratblut erhalten hatten, reagierte mit leichtem Fiebernur einer oder 7,7 % und von denjenigen, welchen natives Blueverabreicht worden war, kein einziger.

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Über die Bluttransfusionen mit frischem und konserviertem Blut im Säuglingsalter.

(Vorläufige Mitteilung.)

Von

N. HALLMAN.

Über den Einfluss des frischen Blutes und des konservierten Zitratblutes auf die Stickstoffbilanz des Organismus.

Besonders bei den Säuglingen ist man oft gezwungen, bei schwerer Diarrhöe und Erbrechungsfällen sogar längere Zeit nahezu die gesamte Flüssigkeit und auch die Nahrung parenteral zuzuführen. Als eine Suspension, welche reichlich und in möglichst geeigneter Form besonders Eiweiss enthält, lässt sich dann die Verabreichung von Blut als Nahrungstransfusion neben den gewöhnlich angewandten Kochsalz- und Glukoselösungen denken. Aus meiner vorigen Arbeit (HALLMAN) ist hervorgegangen, dass das konservierte Zitratblut das rote Blutbild nicht besonders günstig beeinflusst. Diese, ebenso wie einige frühere Arbeiten (BELK und Barnes, Chapin und Ross) weist auf schnellen Zerfall der roten Blutkörperchen hin. Es ist sehr interessant und auch praktisch wichtig, etwas über das Schicksal des Eiweisses sowohl der roten Blutkörperchen als auch des Gesamtblutes nach der Transfusion zu wissen. Es ist möglich, dass der Organismus für ihn wichtige Bestandteile in dieser oder jener Weise ausnutzt. Indem wir die Ausscheidung des Gesamtstickstoffs verfolgen, erhalten wir eine Auffassung von dieser Frage. Die einzigen bei Menschen ausgeführten Stickstoffbilanzversuche im Zusammenhang mit Bluttransfusionen, die ich in der Literatur gefunden habe, sind die von den Russen Fedorow, Baruline und NamiatSCHEFF vorgenommenen Untersuchungen mit frischem und konserviertem Zitratblut. Im ersteren Falle rief die Transfusion eher Verminderung der Ausscheidung von Stickstoff hervor, im letzteren war das Ergebnis ganz umgekehrt.

Über die Untersuchungsmethode.

In der vorliegenden Untersuchung ist die Ausscheidung von Stickstoff vor und nach der Bluttransfusion bestimmt worden, indem der Harn und die Fäzes von Säuglingen gesammelt wurden. Ausser im Harn und im Stuhl wird Stickstoff auch mit dem Schweiss ausgeschieden, aber die Abscheidung ist im Vergleich zu den ersteren so klein, dass man sie ausser acht lassen kann. Schweiss wird in aufeinander folgenden Tagen ungefähr gleichviel abgesondert. Die Untersuchungsobjekte sind während der ganzen Observationszeit in der Schwebe festgebunden gewesen, wo die Bewegung in grösserem Umfange unmöglich, und damit auch die Schweissabsonderung möglichst gering ist. Wenn sie sich einmal daran gewöhnt haben, befinden sich die Säuglinge auch festgebunden ziemlich wohl, und sie machen nach den ersten Tagen keine nennenswerten Anstrengungen sich zu befreien (Ekzem-Kinder).

Während der Observationszeit ist versucht worden, die Nahrung, soweit möglich, so zu halten, dass sie dem Alter entspricht. Die Flüssigkeitsmenge ist die ganze Zeit begrenzt gewesen. Die Stickstoff- und also die Eiweissmenge wurde allerdings möglichst niedrig gehalten und der Energiebedarf durch Zucker und Fett ersetzt. Im allgemeinen betrug die Kaloriemenge der Nahrung ungefähr 100 Kal. pro Körpergewichtkilogramm. Die Stickstoffbilanz war mit einer einzigen Ausnahme positiv.

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Die täglichen Stickstoffbestimmungen sowohl aus den Ausscheidungen als aus der Nahrung und auch dem übertragenen Blut wurden nach der Mikro-Methode von KJELDAHL durchgeführt.

Das Blut wurde entweder direkt oder nach Zusatz von Zitrat (10 % 2,5 %ige Na-Zitratlösung) und der zur Sache gehörigen Konservierung in die oberflächlichen Venen des Kopfes infudiert.

Die Versuchsobjekte wurden unter solchen Patienten ausgewählt, deren Hämoglobin zwischen 50—70 % Sahli schwankte, so dass die Transfusion auf keinen Fall Polyglobulie verursachen konnte.

Die Untersuchungen mit frischem Blut.

Frisches Blut wurde fünf Säuglingen verabreicht. Von diesen erhielten zwei direkt vom Spender mit Hilfe paraffinierter Spritzen entnommenes Blut und die restlichen drei frisches Zitratblut.

Aus Tabelle 1 ist die Menge des dem Organismus zugeführten und des ausgeschiedenen Stickstoffs während einer ebenso langen Zeit vor und nach der Bluttransfusion ersichtlich. Im allgemeinen wurde die Ausscheidung 6-8 Tage verfolgt, in welcher Zeit die nach der Übertragung möglicherweise eingetretenen Veränderungen wieder auf das Niveau vor der Transfusion zurückgegangen sind. Wie man sieht, ist die Stickstoffretention regelmässig vor der Transfusion etwas grösser gewesen als danach. Nur in Fall Nr. 3 ist sie gleich geblieben. In der Tabelle ist indessen der in dem infudierten Blut enthaltene Stickstoff garnicht berücksichtigt. Wenn man diesen mit den Differenzen der Retention in den verschiedenen Fällen vergleicht, so sieht man, dass die zugeführte Menge regelmässig grösser gewesen ist als die Verminderung der Stickstoffretention (Tabelle Nr. 2). Bei Berechnung auf Grund dessen erhält man als Wert des retinierten Stickstoffs aus dem übertragenen Blut 54.4-101 %.

Irgendein Unterschied zwischen dem nativen Blut (Fall Nr. 1 und 2) und dem frischen Zitratblut (Fall Nr. 3, 4 und 5) lässt sich nicht feststellen. Von dem Stickstoff beider Blutsorten nutzt der Organismus die gleiche Menge aus. Das Resultat lässt sich sehr gut meinen früheren Untersuchungsergebnissen über das Blutbild gleichstellen. Zur Kontrolle sind auch in diesen Fällen regelmässig Hämoglobinbestimmungen des Blutes durchgeführt worden. Ausnahmslos ist das Hämoglobin sofort nach der Transfusion gestiegen und trotz einer kleinen vorübergehenden Senkung deutlich höher als ursprünglich geblieben. — Es sei noch erwähnt, dass das Gewicht der Patienten nach den täglichen Wiegungen regelmässig zugenommen hat.

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Nr. der Versuchs- serie	Art des	In der Na	hrung g N.	Im Harn g N.			
	Blutes	Vor der Infusion	Nach der Infusion	Vor der Infusion	Nach der Infusion		
1	Nativ	18,93	18,16	8,05	8,25		
2	30	15,60	14,28	8,74	9,10		
3	Zitrat	19,19	18,49	6,84	6,71		
4	30	15,97	16,25	4,89	6,62		
5	39	15,80	14,28	8,18	8,14		

Tabelle Nr. 2.

Nr. der Versuchsserie	g N im infundierten	Einfluss der Blutübertragung auf die N-retention	Von N des infundierten Blutes retiniert				
	Blut	± g	g	%			
1	2,24	-0,45	1,79	80,0			
2	2,91	-1,16	1,75	60,1			
3	2,06	+0,02	2,08	101,0			
4	2,41	-1,10	1,81	54,4			
5	3,01	-0,33	2,68	89,0			

Bedauerlicherweise kann ich wegen Platzmangel mein Versuchstagebuch nicht vollständig wiedergeben, sodass ich mich mit einigen allgemeinen Beobachtungen begnügen muss. In der Harnmenge zunächst lassen sich keine regelmässigen Schwankungen feststellen. Kein einziges Mal ist die Harnmenge am Tage nach der Transfusion grösser gewesen als am vorhergehenden. Im Vergleich zu der täglich verabreichten Flüssigkeitsmenge (900—1 000 ccm) ist die Blutmenge auch verhältnismässig gering (80—110 ccm). In der Menge des Stuhls und des Harns ebenso wie im abgesonderten Stickstoff treten natürlich täglich Variationen auf, aber sie sind verhältnismässig klein, und die Letzteren sind teilweise auf die Schwankungen des täglich in der Nahrung enthaltenen Stickstoffs zurückzuführen. Die Ausscheidung von Stick-

Im Stuhl g N.			neidung mt g N.	N-retention in g			
Vor der Infusion	Nach der Infusion	Vor der Infusion	Nach der Infusion	Vor der Infusion	Nach de Infusion		
1,94	1,86	10,01	9,65	8,92	8,51		
2,10	1,58	10,84	10,68	4,76	3,60		
1,48	1,26	8,77	7,97	10,42	10,52		
2,50	2,27	7,39	8,89	8,70	7,36		
2,58	1,94	10,77	10,04	4,58	4,20		

stoff nimmt, wenn man sich so ausdrücken kann, in Form des Harnstickstoffs zu (Fall Nr. 1, 2, 3 und 4). Der Stickstoff des Stuhls hat regelmässig nach der Blutübertragung eher abgenommen.

Die tägliche Stickstoffretention ist vor der Transfusion verhältnismässig gleichmässig geblieben. In den Tagen nach der Blutübertragung sind darin kleine Schwankungen wahrzunehmen, in welchen jedoch keine Regelmässigkeit zu beobachten ist. Die Bluttransfusion bringt die Stickstoffausscheidung gewissermassen etwas aus dem Gleichgewicht.

Die Untersuchungen mit konserviertem Zitratblut.

Konserviertes Zitratblut (5—14 Tage) ist 5 Säuglingen verabreicht worden. Im Gegensatz zu den früheren Patienten hat einer davon während der Observationszeit stickstofffreie Nahrung erhalten (Fall Nr. 7). Da man die Untersuchung nicht sehr viel in die Länge ziehen kann, sind hier vor der Transfusion nur drei Tage beobachtet worden, in welcher Zeit die Stickstoffbilanz stabilisiert gewesen ist.

Wenn man die erhaltenen Resultate betrachtet (Tabelle Nr. 3), sind die Versuchsserien zunächst einmal in zwei Gruppen einzuteilen. In die erste werden diejenigen gerechnet, wo alles normal verlaufen ist (Fall 6, 8, 10), und in die zweite diejenigen, wo das Versuchsobjekt während der Zeit der Observation Durch-

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Nr. der Versuchs- serie	Konser- vierungszeit	In der Na	hrung g N.	Im Harn g N.			
	Tage	Vor der Infusion	Nach der Infusion	Vor der Infusion	Nach de Infusion		
6	10	24,29	25,41	12,53	14,58		
7	10	0,60	1,01	2,64	5,22		
8	14	18,46	17,11	10,05	11,46		
9	14	18,46	17,11	10,36	8,46		
10	5	15,72	14,36	4,10	4,87		

fall bekommen hat. Eigentlich kann man nur die Fälle der ersten Gruppe zum direkten Vergleich mit den mit frischem Blut durchgeführten Versuchen benutzen, aber aus Gründen, die unten näher auseinandergesetzt werden, habe ich es für angebracht angesehen, auch die Letzteren näher zu behandeln. Der Durchfall ist in keinem von den beiden Fällen so schwer gewesen, dass er eine Unterbrechung der Versuchsreihe verursacht hätte.

Zunächst sieht man, dass die Stickstoffretention in denjenigen Fällen (Nr. 6, 8, 10), welche ohne Komplikationen verlaufen waren, nach der Transfusion deutlich kleiner gewesen ist als vorher (Tabelle Nr. 3). Von dem Stickstoff des infudierten Blutes wurden in einem Fall 16 % retiniert, im zweiten 2,2 % und im dritten 39,6 %, d. h. die Blutübertragung hat in diesem dritten Fall eher Zunahme der Stickstoffausscheidung hervorgerufen, ausser dass der in dem infudierten Blut enthaltene Stickstoff ausgeschieden wurde (Tabelle Nr. 4). Die Konservierungszeit scheint, wenigstens sofern sie 5 Tage nicht überschreitet, keine Bedeutung zu haben.

Die tägliche Retention ist mit Ausnahme eines Falles (Nr. 6) vor der Blutübertragung ziemlich gleichmässig geblieben. Dieser Patient erhielt relativ viel Eiweiss enthaltende Nahrung (²/₃ Milch), aber das endgültige Resultat ist dessen ungeachtet das gleiche wie in den anderen Serien. Nach der Transfusion treten in der Retention Schwankungen in negativer Richtung ein. Sofort im Verlauf der nächsten 24 Stunden ist die Retention ver-

Im Stuhl g N.		Ausscheidung insgesamt g N.		N-retention in g	
Vor der Infusion	Nach der Infusion	Vor der Infusion	Nach der Infusion	Vor der Infusion	Nach der Infusion
1,46	2,12	13,96	16,65	10,33	8,76
0,74	1,47	3,88	6,69	-2,78	-6,59
2,18	2,44	12,28	13,91	6,33	3,05
2,50	3,25	12,76	11,02	5,80	6,09
3,50	3,56	7,60	7,41	8,12	5,98

Tabelle Nr. 4.

Nr. der Versuchsserie	g N im infundierten Blut	Einfluss der Blutübertragung	Von N des infundierten Blutes retiniert	
		± g	g	%
6	1,87	-1,57	0,80	16,0
7	2,84	-2,81	0,03	1,1
8	2,35	-3,28	-0,93	-39,6
9	2,35	+0,29	2,64	112,3
10	2,24	-2,19	0,05	2,2

ringert, aber das Minimum wird an verschiedenen Tagen erreicht. Nach Verlauf von 6—8 Tagen werden regelmässig Werte von der gleichen Grössenklasse wie vor der Übertragung erreicht.

Die Harnmenge zeigt auch in diesen Fällen keine Regelmässigkeit. In allen drei Fällen ist die Stickstoffausscheidung im Harn deutlich grösser gewesen als früher. Auch mit dem Stuhl ist mehr Stickstoff ausgeschieden worden, aber den relativ grösseren Anteil an der Vermehrung hat doch der Stickstoff des Harns.

Das Hämoglobin ist übereinstimmend mit meinen früheren Versuchen kein einziges Mal durch die Transfusion gestiegen. — Bei allen Patienten dagegen nahm das Gewicht regelmässig zu. — Kein einziges Mal folgte auf die Transfusion eine Reaktion.

Eine Ausnahme bilden die Fälle (Nr. 7 und 9), wo während der Observation Diarrhöe auftrat. Da die Nahrung trotz des Durchfalls nicht nennenswert geändert wurde (bei dem einen Fall überhaupt nicht), wäre anzunehmen, dass die Ausscheidung des Stickstoffs beim Beginn des Durchfalls vor allem in Form von Darmflüssigkeiten zunähme. In beiden trat die Diarrhöe in den nächsten Tagen nach der Transfusion ein. Die Normalsituation vor der Blutübertragung lässt sich also leicht direkt mit der darauffolgenden vergleichen.

Wir behandeln zuerst Fall Nr. 7, wo der Patient nahezu stick stofffreie Nahrung erhalten hatte (0,3 g Stickstoff pro Tag). An zweiten Tag nach der Blutübertragung bekam der Patient Durchfall. Die mit dem Harn ausgeschiedenen Stickstoffmenge war an Tage nach der Transfusion von 0,34 g am vorhergehenden Tage auf 0,88 g gewachsen, während die Harnmenge gleich blieb. Am ersten Durchfalltag nahm die Harnmenge auf ca. 1/4 ab, und die Stickstoffausscheidung darin blieb unverändert. Wegen des schlechten Allgemeinzustands wurde die Verabreichung von Nährlösung nun abgebrochen. Stattdessen wurde 10 % mehr Zuckerwasser gegeben als der Patient früher Flüssigkeit erhalten hatte. Nachdem der Zustand sich gebessert hatte, wurde am 4. Tage wieder zur gleichen Flüssigkeitsmenge wie vor dem Durchfall übergegangen. Am sechsten Tage nach der Bluttransfusion war die Ausscheidung im Harn und auch die Harnmenge auf dem gleichen Niveau wie vor der Blutübertragung. Während der Zeit des Durchfalls hatte sich die Stickstoffausscheidung im Harn nahezu verdoppelt. - Stuhlgang hatte der Patient reichlich zunächst nur in den Krankheitstagen, wo die Stickstoffmenge der Fäzes im Vergleich zu früher das Zehnfache betrug, d. h. mit dem Stuhl wurde 1,0 g Stickstoff ausgeschieden. — Wie aus der Stickstoffbilanz ersichtlich ist (Tabelle Nr. 4) genügt der mit der Blutübertragung zugeführte Stickstoff vollständig zur Kompensation des durch den Durchfall verursachten Stickstoffverlustes. Nach den vorigen Serien hätte die Stickstoffabsonderung in diesem Falle reichlicher sein müssen. Erstens hätte die dem Stickstoff des infudierten, 10 Tage lang aufbewahrten Blutes entsprechende Menge ausgeschieden werden müssen, wozu noch die durch die

Diarrhöe bedingte Ausscheidung hinzugekommen wäre. Die reichlicher als sonst verabreichte Flüssigkeit hat sicherlich auch den möglicherweise in den Gewebe zurückgebliebenen Stickstoff mitgespült, so dass sich die Verminderung der Ausscheidung auch dadurch nicht erklären lässt. Am letzten Observationstag entsprach die Ausscheidung des Stickstoffs ausserdem den Werten vor der Blutübertragung.

In Fall Nr. 9, wo 14 Tage lang aufbewahrtes Blut gegeben wurde, trat der Durchfall einige Stunden nach der Transfusion ein. Der Allgemeinzustand war jedoch so gut, dass es nicht notwendig war, während der Versuchsreihe von der üblichen Kost (1/2 Milch) und Flüssigkeitsmenge abzuweichen. Die schon früher verhältnismässig reichlichen Stühle verdoppelten sich sofort bei Beginn des Durchfalls und wurden ausserdem schleimig und übelriechend. Die Harnmenge nahm in den ersten Tagen ab und desgleichen der darin ausgeschiedene Gesamtstickstoff. In den Stühlen war die Stickstoffausscheidung nahezu verdoppelt. Zusammengerechnet zeigte die Stickstoffbilanz jedoch keinerlei Veränderungen, wenn man die Werte vor und nach der Blutübertragung miteinander vergleicht. Der ganze Stickstoff des infudierten Blutes scheint retiniert worden zu sein. Es ist allerdings zu bemerken, dass der Patient in den ersten Tagen der Diarrhöe sich dann und wann erbrach, aber die Erbrechungen waren sehr gering, so dass sie das Endresultat nicht sehr beeinflussen konnten. Erwähnt sei noch, dass die Blutübertragung auch bei diesen Fällen die Hämoglobinwerte in keiner Weise beeinflusste.

In den beiden Fällen, wo während der Zeit der Versuchsserie nach der Bluttransfusion Diarrhöe eingetreten ist, weicht die Stickstoffausscheidung also ab von den anderen Fällen, wo die Patienten konserviertes Zitratblut erhalten hatten. Bei den Letzteren nahm die Stickstoffausscheidung dem Stickstoff des infudierten Blutes entsprechend zu. Bei den Ersteren wiederum, wo zu erwarten gewesen wäre, dass der Durchfall umgekehrt vermehrte Ausscheidung hervorgerufen hätte, hatte die Blutübertragung in dem einen Falle gar keine Wirkung, und bei dem anderen war die Ausscheidung nicht grösser als bei denjenigen Patienten, die keine Diarrhöe-Komplikationen gehabt hatten.

Besprechung der Ergebnisse.

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Ehe wir daran gehen, die erhaltenen Resultate näher zu besprechen, muss erst geklärt werden, welchen Wert man den Stickstoffbilanzversuchen beimessen kann. Aus früheren bei Säuglingen durchgeführten Untersuchungen (EDELSTEIN und LANG-STEIN) wissen wir, dass trotz ganz gleichen Stickstoffgehalts der Nahrung die Ausscheidung im Stuhl und im Harn an aufeinander folgenden Tagen nicht ganz gleichgross ist. Nach den erwähnten Autoren erhält man sogar auch dann, wenn man in dreitägigen Perioden rechnet, in nacheinander folgenden Perioden keine gleichgrossen Werte. In diesen Versuchen ist jedoch Nahrung verabreicht worden, welche verhältnismässig reichlich Eiweiss (Kasein) enthielt. Einer von meinen Patienten erhielt ebenfalls relativ reichlich Eiweiss enthaltende ²/₃-Milchmischung (Fall Nr. 6). und die Ausscheidung schwankte, wie schon erwähnt wurde, täglich verhältnismässig viel. Die übrigen dagegen bekamen Nahrung, welche weniger Eiweiss als normal enthielt, und die Stickstoffausscheidung ist dann relativ gleichmässig gewesen. Da ich in meinen Versuchsserien regelmässig in gleicher Richtung gehende Resultate erhalten habe, dürfte es kaum notwendig sein, den täglichen geringen Schwankungen bei der Beurteilung des Endergebnisses grössere Bedeutung beizumessen.

Zweitens wissen wir, dass grosse Flüssigkeitsmengen an sich die Stickstoffausscheidung vermehren (Neumann). Der Abbau von Eiweiss wächst allerdings nicht, sondern es handelt sich um irgendeine »Ausschwemmung». In meinen Versuchen ist die unfudierte Flüssigkeitsmenge (80—120 ccm) im Vergleich zu der täglich enteral verabreichten (900—1000 ccm) relativ klein. Ausserdem wird auch dieser Faktor eliminiert, wenn man die mit frischem und mit konserviertem Blut erhaltenen Resultate miteinander vergleicht.

Wenn man dann die mit frischem und die mit konserviertem Zitratblut erhaltenen Resultate miteinander vergleicht, stellt man fest, dass darin ein deutlicher Unterschied besteht. Bei denjenigen Patienten, welche frisches Blut oder frisches Zitratblut erhalten hatten, wurde der grösste Teil des in dem infudierten Blut enthaltenen Stickstoffs retiniert, welches Resultat dem parallel stattfindenden Anstieg des Hämoglobins entspricht. Bei denjenigen wiederum, welche konserviertes Blut (Konservierungszeit 5—14 Tage) erhalten hatten, hatte die Stickstoffausscheidung zugenommen, sodass es den Anschein hatte, als ob der ganze Stickstoff des infudierten Blutes in den nächsten Tagen ausgeschieden worden wäre. Die Stickstoffausscheidung hat besonders im Harn, aber auch im Stuhl zugenommen. Eine Ausnahme unter den Letzteren bilden die zwei Fälle, wo in den Tagen nach der Biutübertragung Durchfall aufgetreten ist. Bei dem einen davon nahm die Ausscheidung überhaupt nicht zu, bei dem anderen wiederum war sie nicht grösser als auch bei den übrigen Patienten, welche konserviertes Zitratblut erhalten hatten, dessen ungeachtet, dass der Durchfall vermehrte Ausscheidung vorausgesetzt hätte.

Die Resultate entsprechen den von den Russen Feodorow, BARULINE und NAMIATSCHEFF bei Erwachsenen erhaltenen Ergebnissen sowohl mit frischem Blut als auch mit konserviertem Zitratblut. Von den erwähnten Untersuchungen stehen bedauerlicherweise nur Referate zur Verfügung, sodass ein exakterer Vergleich unmöglich ist. Im Gegensatz zu diesen Untersuchungen ist die Stickstoffbilanz in meinen Versuchen die ganze Zeit positiv gewesen, so dass die Letzteren also mehr normalen Verhältnissen entsprechen. - Von früheren Tierversuchen seien die Hundeversuchen von Hari erwähnt, wo die Stickstoffausscheidung nach Transfusionen von frischem Blut zunahm, wenn die Tiere gewöhnliche Nahrung erhielten. Bei Hungerhunden dagegen stieg die Stickstoffausscheidung nicht. Lombrosa und Zummo ihrerseits haben drei Hunden mehrere Blutübertragungen mit frischem Blut nacheinander gegeben, wobei die Ausscheidung nur in einem Falle stieg. Die Resultate gehen also in gewissem Masse in verschiedener Richtung.

Aus ernährungschemischen Untersuchungen wissen wir, dass der Organismus der Kinder, insbesondere der Säuglinge, mehr Stickstoff zu retinieren vermag, wenn dieser in der Nahrung reichlicher enthalten ist. Die Ausscheidung steigt zwar, gleichzeitig aber auch die retinierte Menge (Brock). Bei der Untersuchung

von Brust- und Flaschenkindern ist festgestellt worden, dass die Stickstoffretention bei den Letzteren beständig grösser ist als bei den Ersteren (ROMINGER und MEYER). Die Kuhmilch enthält bekanntlich mehr Eiweiss als die Muttermilch. Bei Erwachsenen dagegen nimmt die Retention trotz zusätzlicher Stickstoffveralt reichung nicht zu. Wenn wir zu mehr Stickstoff enthaltender Nahrung übergehen, erreichen wir nicht gleich die Maximumreten tion. Der Organismus braucht gewisse Zeit (nach HAWKS, BREV und Dyc 9 Tage), um sich daran zu gewöhnen, genügend Stickstoff aufzunehmen. Während dieser Zeit ist die Ausscheidung verhältnismässig gross. Ganz das Gleiche, nur im umgekehrten Sinne, geschieht dann, wenn wir zu weniger Stickstoff enthalterder Nahrung übergehen.

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Wenn man frisches, lebensfähiges Blut i. v. verabreich. nimmt die Stickstoffausscheidung nicht zu, und der Organismus ist offensichtlich imstande, es als solches wenigstens zum grössten Teil zu verwerten. Die roten Blutkörperchen bleiben im Gfässsystem (Belk und Barnes), ihre Anzahl sowie die Hämoglobinmenge nimmt zu (HALLMAN) usw. Das Volumen des Blutes dagegen geht bald auf das frühere Niveau zurück (BAKVIN, ASTROV und RIVKIN, SIBLEY und LUNDY u. a. m.). - Zahlreiche Forscher haben die Ausscheidung des Urobilins verfolgt, aber die Resultate sind ziemlich widersprechend gewesen (OPITZ und CHOREMIS, PELLEGRINI, KÜHL u. a. m.). Nach OPITZ und KLINKE wächst bei Kindern nach der Transfusion die Ausscheidung von Harnstoff, was ihres Erachtens auf dem Abbau des Eiweisses des Plasmas beruht. Den kleinen Anstieg in der Stickstoffausscheidung nach der Infusion von frischem Blut könnte man auf Grund dessen erklären, aber diese Angelegenheit ebenso wie die Verfolgung der Urobilinsekretion erfordert noch nähere Untersuchungen.

Wenn man dagegen konserviertes Zitratblut verabreicht, so weisen schon der Blutstatus (HALLMAN), desgleichen die Agglutinationsversuche (BELK und BARNES) sowie die Versuche mit radioaktivem Eisen (CHAPIN und ROSS) darauf hin, dass wenigstens die roten Blutkörperchen zugrunde gehen. Schon dies erklärt die Zunahme der Stickstoffausscheidung, wenn man voraus

setzt, dass der Organismus die entstandenen Abbauprodukte nicht zu fixieren vermag. Die oben erwähnten ernährungsphysiologischen Versuche zeigen, dass der Organismus ohne Gewöhnung nicht imstande ist, den erhöhten Eiweissgehalt der Nahrung auszunutzen. Ganz das Gleiche könnte man sich auch von dem mit dem Blut zugeführten Eiweiss denken, obwohl es in einer für den Organismus möglichst vorteilhaften Form dargereicht wird. Es ist kaum anzunehmen, dass die schlechtere Ausnutzung des Stickstoffs der Nahrung auf der Resorption beruhe, es muss hierfür eine andere Erklärung geben. Über die spezifisch-dynamische Wirkung der Eiweisse wissen wir andererseits, dass sie auch parenteral verabreicht den Energiebedarf und damit die Verbrennung vermehren. Ein Teil der Stickstoffausscheidung kann die direkte Folge lediglich der intensiveren Verbrennung sein.

Sehr interessant ist die Feststellung, dass die Stickstoffausscheidung in denjenigen mit frischem Blut behandelten Fällen, wo wegen des Durchfalls ungewöhnlich grosse Absonderung zu erwarten gewesen wäre, umgekehrt eher vermindert war. Die Stickstoffausscheidung im Stuhl nahm infolge des Durchfalls zweifellos zu, aber so entstand im Organismus plötzlich ein Stickstoffbedarf, der durch die zur rechten Zeit vorgenommene Bluttransfusion befriedigt wurde. Eine Stütze für diese Erklärung sind u. a. Haris Versuche mit Hungerhunden, welche im Gegensatz zu den in normaler Weise ernährten Versuchstieren imstande waren, den Stickstoff des infudierten Blutes auszuwerten. Der Deutsche Duesberg hat durch Verabreichung von Serum und Blut den Stickstoff der grossen Eiweisssekretion einer eiternden Wunde kompensiert. Auch in diesem Falle ist der Stickstoffbedarf im Organismus gross gewesen.

Die blosse Untersuchung der Stickstoffbilanz gibt uns kein klares Bild über das Verhalten des Organismus zu der Blut- übertragung, insbesondere zu den Eiweissstoffen. Wir erhalten so nur eine summarische Auffassung davon und von dem Vorzug des frischen Blutes bei Säuglingen im Vergleich zum konservierten Zitratblut. Untersuchungen zur näheren Klärung der Frage sind geplant.

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r-8 Zusammenfassung: Es ist die Stickstoffausscheidung nach der Infusion von frischem und konserviertem Zitratblut bei Säuglingen untersucht worden.

Das frische Blut und das frische Zitratblut rufen in der Stickstoffausscheidung einen kleinen Anstieg im Vergleich zur Zeit vor der Blutübertragung hervor. Von dem Stickstoff des infudierten Blutes werden jedoch 55,4—101,0 % retiniert. Von dem Versuchsserien sind 2 mit frischem Blut durchgeführt worden und 3 mit frischem Zitratblut.

Von dem 5—14 Tage lang konservierten Zitratblut werde 1—39,6 — —16 % retiniert. Der grösste Teil des Stickstoffs wird im Harn ausgeschieden. 3 Fälle.

Bei 2 Fällen trat in den Tagen nach der mit konserviertend Zitratblut durchgeführten Blutübertragung plötzlicher Durchfall ein. Bei dem einen nahm die Stickstoffausscheidung im Vergleich zu den oben erwähnten Versuchen überhaupt nicht zu, und bei dem anderen schien trotz der Diarrhöe sogar noch der mit dem Blut zugeführte Stickstoff retiniert zu werden. Dieser Umstand wird durch den erhöhten Stickstoffbedarf im Organismus erklärt.

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Purpura fulminans. (Streptococcal Sepsis.)

By

SVEND HEINILD.

Introduction.

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a) er The syndrome of purpura is always dramatic, as a rule, to the physicians as well as to the patient. This is largely due to the fact that certain forms of purpura — the so called purpura fulminans signify a disease that may terminate fatally within a few days, nay, sometimes even within the first 24 hours. In the following a report will be given of such a case of fulminant purpura in an infant in whom a streptococcal sepsis was found post mortem to be the underlying affection. In this connection some remarks will be made on the concept of purpura fulminans.

Historical.

The term »purpura fulminans» was first employed by Henoch in 1886 at a meeting of the Medical Society of Berlin. Two children, 5 and 2 $^{1}/_{2}$ years old had an acute attack of fatal purpura respectively 2 days after a pneumonic crisis and 2 weeks after an eruption of scarlet fever. The lesion was characterized by large bluish to reddish-black ecchymoses, which within a few hours turned into rather hard infiltrations. Henoch was unable to say anything about the etiology and pathogenesis.

During the following years, similar cases were described, among others, by BORGEN (1901), RIESEL (1905), ELLIOT (1909),

¹ Read before the Society of Danish Pediatricians on October 24, 1945.

MACKRIRIK (1912), KÖNIG (1922), KNAUER (1928), MORAWITZ (1926), GLANZMANN (1937) and KUGELMASS (1941). These descriptions have crystallized into the following clinical picture that is now presented in every hematological text-book: The onset of the disease is quite acute, appearing not especially in patients who already are exhausted. In the skin, often within a few hours, some very extensive, bluish-red to black ecchymoses make their appearance, sometimes occupying entire extremities, and rapidly becoming infiltrated. Hemorrhages into the mucous membranes are never seen (in contrast to Werlhof's disease). The hematological findings as to blood platelets and the other factors taking part in the process of clotting are normal, but the capillary resistance is stated to be lowered. The lesion terminates fatally in 1—4 days. If the course is not fatal, the diagnosis is disputable. Autopsy reveals no characteristic changes in the organs.

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Now, however, it is not unusual that a diagnosis in the course of time becomes more comprehensive, the scope of the classical descriptions becoming wider when the original papers no longer are being read. A couple of examples will appropriately illustrate this point: In 1735 Werlhof described the typical dysovarian purpura in women, and now his description has been modified to such an extent that almost any thrombopenia of unknown origin is designated as Werlhof's disease. Similarly, there is a certain tendency to designate every instance of polyarthritis in children as Still's disease, in spite of the fact that Still's (1897) description covered only a special form of a joint lesion characterized by anemia, enlargement of the spleen, polyadenitis and a characteristic, slowly developing, symmetrical swelling of joints of non-osseous character.

Something similar applies to purpura fulminans. Many acute forms of purpura, in which the general condition of the patient is affected noticeably, are erroneously designated as purpura fulminans in the sense of the term employed by Henoch. Experiences show, however, that this lesion often is confused especially with the acute, presumably allergic, thrombopenic purpura, anaphylactoid purpura (purpura Schönlein-Henoch),

erythema multiforme and fulminant meningococcal sepsis (presumably the WATERHOUSE-FRIDERICHSEN syndrome). In the discussion we shall return to the question that the proper recognition of the lesion and early institution of adequate treatment presumably may be of life-saving significance, so that this matter is not merely of academic interest.

Differential Diagnosis in Acute Purpura.

Purpura is a typical rummage diagnosis, covering a most unhomogeneous group of patients. The proper cognition of this fact appears to have been delayed by the circumstance that in text-books these cases are dealt with under the heading of diseases of the blood or hemorrhagic diatheses instead of infection, allergy or endocrine lesions. The systematics of these affections will still have to be based on a mixture of entirely clinical, etiological and pathologic-anatomical points of view. The same applies also to the following schema comprising the diagnoses which in practice will have to be taken into consideration in a given case of acute purpura:

Schematic Survey of Various Forms of Acute Purpura.

With Thrombopenia:

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Essential hemorrhagic thrombopenic purpura.

Allergic » » Aplastic »

Without Thrombopenia:

Simple purpura.

Infectious »

Leukotic

Septic » (meningococcus, streptococcus).

SHÖNLEIN-HENOCH'S purpura.

Erythema multiforme.

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With Thrombopathy:

Hemorrhagic thrombasthenia (GLANZMANN). Constitutional thrombopathy (WILLEBRAND).

Waterhouse-Friderichsen's Syndrome:

Infection (meningococcal sepsis)? Endocrine affection?

The only feature common to all these forms of purpura is their acute onset; they all may become manifest in the course of some hours. Thus this schema includes no chronic forms of purpura as seen, for instance, in certain diseases of the blood, certain well-known disturbances of the coagulation, and avitaminoses. It is easy to understand that, as a rule, inquiry into the history of the patient and hematologic examinations soon will exclude the possibility of certain forms, so that in practice the differential diagnosis will involve merely the following conditions: essential thrombopenic purpura, erythema multiforme, meningococcal sepsis or some other form of sepsis, and WATER-HOUSE-FRIDERICHSEN'S syndrome.

Thrombopenic purpura as well as erythema multiforme have been dealt with in preceding papers (1942, 1944) and will therefore not be mentioned here. The relation between WATERHOUSE-FRIDERICHSEN'S syndrome and meningococcal sepsis is discussed in an interesting paper by Kirketerp (1945). The concept of purpura fulminans, which apparently is missing in the schematic survey above, will be discussed more thoroughly after the following account of the

Writer's Case.

Girl, 3 weeks old. Admitted to the Pediatric Dep., the Rigs Hospital, ²⁴/₅—²⁵/₅, 1945 (Record No. 468/45).

Past History. — The patient is the only child of young parents. Born by natural delivery, crying at once. Weight at birth: 2870 g. The child has had mother's milk exclusively and has been sucking well. At the age of 2 weeks, together with her mother, she made a journey from Sweden to Denmark.

Present Illness. — At the age of 3 weeks $(^{23}/_5)$, in the evening before admission, she commenced to suck poorly, without any prodromata whatever. During the following day (on the day of admission) she has been whining, becoming somewhat weak and flabby, with several thin and slimy stools, while the buttocks became markedly irritated. In the evening a read spot, about $1 \, ^1/_2$ cm in diameter is noticed over the right knee. She is brought to the hospital.

Physical Examination, on Admission, $^{24}/_{5}$ (24 hours after the appearance of the first symptoms): Small child, greyish-pale, markedly intoxicated, with lowered turgor. Apparently no meningitic or pneumonic features.

Fauces: Apparently normal.

Heart and Lungs: No abnormality on auscultation.

Abdomen: Slightly meteoristic, soft.

Skin: The buttocks are flaming read, shiny, moist, reminding of intense diaper rash. The anterior aspect of the right knee-joint is the site of a red, infiltrated, affection, nearly 3 cm in diameter, reminding somewhat of a nevus vasculosus.

Temperature: 36.8°.

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Course. — In spite of stimulants, the child is getting very poorly during the night. In the morning (36 hours after the onset) she is extremely exhausted, greyish-pale, cyanotic, with superficial respiration, presenting the picture of a peripheral circulatory collapse.

Skin: On the lower part of the abdomen, above the symphysis, there is now a bluish-red infiltrated area, 6×8 cm, reminding mostly of a sugillation, surrounded by a halo, less intensely red. The red spot on the right knee appears to be a little smaller than in the evening before. The abdominal wall is rather oedematous, and typical signs of hypostasis are found on the back, at the base of the lungs.

Intensive chemotherapy (alfasol) is instituted; and 100 cc. serum is given intraosseously.

During the following 3—4 hours the skin affection on the abdomen develops so that the central part becomes deeply dark-blue, cyanotic and infiltrated, surrounded by an intensely

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red halo (quite corresponding to the photograph presented in PFAUNDLER & SCHLOSSMANN: Handbuch d. Kinderheilk. I, p. 951). As the lesion now is assumed to be a malignant erysipelas, the child is given 100 cc. scarlatinal convalescent serum intraosseously. But the patient dies an hour later, *i.e.*, about 46 hours after the appearance of the first symptoms.

Autopsy. — On section, the skin affection described is found to be oedematous and moist. In addition, petechiae are seen on the pleural surface, and patches of fibrinopurulent exudate on the oedematous intestines. Otherwise no particularly characteristic findings; especially, no enlargement of the thymus, and no hemorrhage in the adrenals. The spleen and liver show no definite abnormality, except that the liver on the cut-surface appears a little friable and »cloudy».

Cultures from the ascitic fluid, subcutis and liver give growth of hemolytic streptococci.

Epicrisis:

A previously healthy child, 3 weeks old, develops an acute, severe systemic lesion, characterized by the striking skin affection of bluish-black infiltrated purpura. The disease terminates fatally in 46 hours. Post mortem, growth of hemolytic streptococci is obtained in cultures from the skin affection as well as from the liver and the ascitic fluid.

Discussion.

There can hardly be any doubt that here we are faced by a case of acute streptococcus sepsis, presumably originated from an infected diaper rash, and that the accompanying skin affection quite corresponds to the findings previously described as typical of purpura fulminans. Naturally such a case raises the question: Is the classical purpura fulminans always an expression of streptococcal sepsis?

On going through the above-mentioned literature with a view to this point, it is soon realized as a striking fact that at any rate scarlet fever — a principal streptococcus infection — plays a dominating rôle in many case histories, the purpural affection developing 2—4 weeks after the appearance of the rash. This applies, for instance, even to one of the two aforementioned cases reported by Henoch, and also to the cases reported by Riesel, Elliot, Mackririk and Kugelmass. Furthermore, Riesel found that in 12 cases reported up to 1905 the purpura was preceded by scarlet fever in 5. In 1909 Elliot investigated the predisposing cause in 24 cases of purpura fulminans, and found scarlet fever in 11.

Blood cultures have been made only in relatively few other cases reported — as a rule with a negative result. Still, as early as 1901, growth of *streptococci virulent for rabbits* was obtained by Borgen in blood cultures from his patient, a boy of 2 years, who died 60 hours after the onset. Strange to say, this observation appears not to have left any track in the literature. In 1922 König isolated streptococci from the blood of his patient who had a moist eczema of the face and died within 48 hours after the onset. Pulvertaft found hemolytic streptococci in the pleural exudate of one of his patients who had been operated on for empyema, likewise with fatal outcome.

It is a well-known fact, moreover, that in certain rare cases the scarlatinal rash may become hemorrhagic because of damage to the capillaries - something that may be encountered, though in a minor degree, in the Rumpel-Leede test too (Nørby). In subacute streptococcal sepsis (subacute bacterial endocarditis) it happens occasionally that endothelial cells even become detached and may be evacuated together with the peripheral blood, where they may be of some diagnostic significance as »large mononuclears», a phenomenon that is known also from the description of meningococcal sepsis given by Thomsen & Wulff. Finally, Pulvertaft has shown experimentally — based on observations on the effect of streptococcus toxin on rabbits - that all the toxic effects may be explained as endothelial injuries, and that the one condition in human pathology that most fittingly may be parallellized with experimental streptococcal sepsis is just purpura fulminans.

In view of the fact that the more severe forms of universal bacterial infection that take a rapid fatal course not infrequently are accompanied by extensive hemorrhagic exanthema, the conditions mentioned here cannot be taken as accidental. It may safely be looked upon as proved that, in a great majority of cases the classical clinical picture of purpura fulminans is an expression of streptococcal sepsis.

Now, then, is it possible clinically to distinguish between streptococcal sepsis and meningococcal sepsis, when both lesions indeed take the same fulminant course?

Naturally, it would be difficult to gain a considerable personal experience in this respect even though this seems practicable to some extent — at any rate, judging from the literature (Thomsen & Wulff, Stevens, Lassen, Snorrason & Vermehren, Andresen & Gormsen, Nielsen & Nørby). For the violent, bluish-black, infiltrated ecchymoses, sometimes with vesiculation, surrounded by a red halo are specific of streptococcal sepsis, whereas meningococcal sepsis usually is associated with more scattered petechiae or minor ecchymoses, even though this is no reliable criterion (Stevens). Presumably, further observations with a view to this very point will be able to settle the question. It is to be mentioned that at present it seems most likely that the so called Waterhouse-Friderichsen's syndrome is an expression of a meningococcal sepsis, not an endocrine lesion (cf. Kirketerp).

Furthermore, undoubtedly many of the cases of purpura fulminans reported in the literature have been diagnosed erroneously, being actually instances of erythema multiforme (see the description of this disease as an acute infectious lesion given by Seidlmayer, Keil, Heinild, Jersild). It will be proper, for instance, to refer to the cases reported by such an authority as Glanzmann (1937). The photographs reproduced in his paper make the diagnosis erythema multiforme more likely—and, indeed, the patient recovered. At any rate it is quite wrong to look upon purpura fulminans as an acute form of Weelhof's disease. The two morbid conditions constitute essentially different lesions.

Conclusions.

So it is highly probable — almost certain — that the classical purpura fulminans most often — perhaps always — signifies a streptococcal sepsis.

The therapeutic consequence of this will be that every patient with this lesion should immediately, from the very first observation, be treated intensively with chemotherapy — for instance, with a dosage (twice the pneumonic dose) recommended by LASSEN, SNORRASON & VERMEHREN in meningococcal sepsis.

In future, penicillin therapy should not be left untried.1

Scarlatinal convalescent serum may hardly be of any value in such cases, as the serum merely is antitoxic, not bactericidal. It is to be kept in mind that fully developed purpura fulminans is a disease which without treatment invariably will lead on to the death of the patient within a few days.

For the sake of systematology, in future, efforts should be made in every case to ascertain whether the lesion involves a streptococcal sepsis, and the case ought to be reported — also with reference to the effectivity of the treatment.

As to the differential diagnosis, especially the infectious, relatively benign, form of erythema multiforme should be kept in mind.

Summary.

A brief historical outline is given of the development of the concept of purpura fulminans, and the differential diagnosis is mentioned.

The writer reports the case of a previous healthy, sucking infant, 3 weeks old, who died within 48 hours after the appearance of the first symptoms of the lesion. Autopsy revealed the presence of a streptococcal sepsis, presumably originating from an infected diaper rash.

On the basis of the literature, it is pointed out that it is most

¹ In the discussion following the reading of this paper Professor Siwe' Lund, stated that he had cured a patient suffering from purpura fulminans' likewise produced by a streptococcal sepsis, with large doses of penicillin.

likely that the classical purpura fulminans usually, perhaps always, is an expression of a streptococcal sepsis.

The therapeutic consequence of this will be at once — at the very first observation of the lesion — to institute an energetic chemotherapy; and treatment with penicillin should never be omitted.

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Pubertas Praecox.

Account of a Case of the Constitutional Type in a three year-old Girl.

By

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The early development of the sex characteristics is an abnormal condition due to known and unknown causes. The known causes are: tumors of the gonads and adrenals, and various kinds of lesions of the brain. Each of these primary affections presents typical features in the clinical picture, and may constitute a serious danger for the child, as these affections often are of a malignant nature and may be fatal. Some cases of pubertas praecox, however, present but few and faint, if any, morbid symptoms, apart from the abnormal development, and the general health of such children is apparently quite unaffected. In cases of this sort, there is less reason to be anxious about the viability of the child than about the social and psychic difficulties to which the condition gives rise in youth.

Such a case, which I have followed for more than three years, will be reported in the following.

Elise P. was born on the 24 of March, 1942, as the first child of healthy parents. There are no known cases of pubertas praecox in the family; the mother menstruated since her 13th year. The birth was normal; the child weighed 3 kilos, her height being 51 cm. There were neither spasms, cyanosis nor other signs of brain lesion.

When she was 8 months old, I was called in because she had had whitish discharge from vulva, at intervals of 3—4 weeks.

At that time, already, there was slight hypertrophy of the breasts, and pubes were definitely more pronounced than normal. A month later the increase in the size of the breasts was indubitable, and there was pigmentation of areolae and obvious linea fusca. The discharge was now sanguinolent, the mucosa of vulva was somewhat succulent, but there was no clitoric hypertrophy, nor was any tumor in the abdomen disclosed by palpation or by rectal examination. Moreover she was a rather big and somewhat limp child, without signs of rickets.

Apart from the pubertas praecox, she has been practically in good health afterwards. She has had regular menstruation (3—4 days every 4—5 weeks), and during such periods she has generally been irritable and difficult to manage. The size of the breasts and the amount of pubic hair have increased but moderately. She has grown enormously, and has become tall and slender. She was late in walking, but her static development has otherwise been normal. Despite the rapid growth the teething was late, her first tooth cutting in the tenth month.

She learned to speak early, being psychically a bright child. Recently, however, she has become somewhat shy, timid, unbalanced and restless. She does not care to play with other children or with dolls, preferring to take walks and play 'the lady'. She is not interested in boys.

As her condition seemed to indicate exploratory laparotomy, she was admitted to department C of the Rigshospital on the 8th of June 1945. She was then 3 years and 3 months old. The objective examination gave the following results:

As shown in Fig. 1, she was tall and slender, of harmonious development and with distinct enlargement of the breasts looking like a 'miniature woman'. Her height measured 108 cm equivalent to normal height at the age of 5 years, her weight was 18 kilos.

Roentgenograms of the extremities disclosed an osseous development corresponding to that of a child 10 years old (Fig. 2).

Her face had a somewhat peculiar expression with strikingly deep-set eyes and hollow orbits, and there was very slight hypoplasia of the left half of her face. Examination of the lungs and



Fig. 1.

the heart showed normal conditions. The abdomen was normal, without palpable tumor even on palpation under narcosis. The development of her breasts was equivalent to that of a girl at the age of puberty; the areolae were pigmented. Pubes were well developed. Vulva was normal, especially there was no hypertrophy of the clitoris. Rectal examination disclosed no abnormal masses, uterus and the ovaries were regarded as being of normal size.





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Fig. 2. X-rays of the hands of the patient (left) and of a normal child of the same age (right).

The neurological and ophthalmological examinations disclosed no symptoms of nervous affection. X-ray examinations of the skull and abdomen, and intravenous pyelography showed normal conditions.

Laboratory Data: Hb.: 82 per cent, Mantoux (1 mgm.) negative. Blood-pressure: 90/50, 125/80, 115/70, 105/60.

The urine was normal, the diuresis small, measuring between 160 and 400 cc., but no doubt some of it was lost. The specific gravity of the urine varied between 1.012 and 1.030, most frequently being 1.025—1.030.

Fasting blood sugar 74 mg per hundred cubic centimetres.

A sugar tolerance test was normal. Serum cholesterol 120 mg per hundred centimetres.

Studies on the hormonal excretion in the urine was performed 6 times altogether, with specially careful titration thanks to Dr. Chr. Hamburger's interest in the case. Gonadotropic hormone was not found (always less than 50 M.U.). The presence of estrogen was as a rule demonstrable, but always below 20 M.U. The presence of androgen was generally demonstrable too, though less than 1 international unit. Dr. Chr. Hamburger opines that

the excretion of estrogen is greater than would be anticipated in a child of that age, and that this is suggestive of increased ovarial function.

Thus it is here a question of a girl, aged 3 ½, who, since about her sixth month, has presented distinct signs of pubertas praecox of the feminine type, characterized by precocious menstruation, hypertrophy of the breasts, growths of pubes, and advanced osseous development. She is now a child with a harmonious feminine contour of body, without virile traits, and looking like a miniature edition of a girl at the age of puberty.

Where a case of pubertas praecox is encountered, it is a point of the greatest importance to find the cause of the condition in order to be able to form an estimation of the child's future prospects, the danger of the disease, and the possibilities of effective therapy.

A review of all the cases of pubertas praecox on record in the literature was published in 1938 by BING, GLOBUS & SIMON. They have found 544 cases, of which 130 were boys and 414 girls. In 104 of these cases the cause of the abnormality had been established either by operation or by autopsy. 44 cases (11 boys and 33 girls) had adrenal tumor, 42 cases ovarian tumor, 13 cases (12 boys and 1 girl) cerebral affections, 4 cases testicular tumor, and 1 case tumor of the prostata. This group of 104 cases, in which the cause of the abnormal condition was established, of course affords better material for an investigation into the nature of pubertas praecox, than the other group of 440 cases, concerning which only clinical observations are available. The former group includes only cases in which the pubertas praecox was associated with symptoms of malign local affections entailing death or indicating operation, whereas the latter group includes, amongst others, cases devoid of such symptoms. From a patho-physiological point of view, this group is just as interesting as the former.

The commonest cause of pubertas praecox in girls is an ovarian tumor, and in most cases it is of the granulosa cell type. These tumors may be of rapid growth and very malign, but as a rule they are fairly benign, so that an operation may result in

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complete recovery with regression of all the symptoms of pubertas praecox. The tumor may occur at any age, both in adults and in children. Gross reports a case in which the symptoms appeared when the child was 5 months old, and Lull has removed such a tumor in a 9 month-old girl. Other cases were reported by Bland & Goldstein, Novak, Parks, Mannheimer and Mengert.

The chief symptoms of this form of pubertas praecox are:
1) growing abdominal tumor, 2) hypertrophy of the breasts, nipples and genitals, and growth of pubes, 3) discharge of blood from vagina, 4) excessive excretion of estrogen in the urine. Besides, accelerated growth with early development of bone nuclei is often seen. This symptom is uncertain, however, and it is not found in all cases.

The estrogen excretion seems in all cases of granulosa cell tumor to be increased, though in greatly varying degrees. Unfortunately, hormone examinations have been performed in rather few cases. Palmer, in previously reported cases, found values from 65 to 17 300 M. U. per litre, in the case reported by Gross he found 17 500 M. U. per 24-hour period, and in Mengert's case 1 000 M. U. per litre were found.

Besides these tumors, simple follicular cysts seem in some cases to give rise to pubertas praecox. Lull, in addition to a typical case of pubertas praecox with granulosa tumor, mentions a 22 month-old girl with scanty menstruation and growth of pubes, but without hypertrophy of the breasts, and with normal skeletal development, in which a cyst measuring 3 by 1 by 1 cm, described histologically as a follicular cyst, was removed by operation. There was no excretion of estrogen. The disappearance of the symptoms after the operation indicates that the cyst has been of decisive importance for the progress of the disease. Lull himself writes that it is hard to account for the clinical picture. I certainly agree with him, for it would be natural to interpret the cyst as being secondary to a more central disturbance.

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Two cases of pubertas praecox as a consequence of chorion-epithelioma of the ovaries were described by Fasold and Sieg-

MUND. In both cases there was menstruation, though often of metrorrhagic type, hypertrophy of the breasts, increased growth of pubic hair, and advanced bony development, as well as copious excretion of gonadotropic hormone (in Siegmund's case from 30 000 to 60 000 M.U.). In both cases the tumor was rapidly metastasizing and growing, and causing death. Arrhenoblastoma of the ovaries may cause a considerable modification of the sex character, though always with a masculinizing effect with retrogression of feminine features. These tumors, which moreover are never met with in early childhood, are thus without importance for the discussion of this case.

Next to the ovarian tumors, the adrenal tumors are the most frequent cause of pubertas praecox. In most cases, however, the hormonal influence is of virilizing character, so that, in boys, an isosexual pubertas praecox develops, whereas, in girls, the result is a heterosexual pubertas praecox. If the influence asserts itself already during fetal life, girls are born as pseudo-hermaphrodites.

The most typical symptom in girls is clitoric hypertrophy, strong hairiness, not only of the genitals, but also of the trunk, the face and of the limbs; strong, square-built stature, and advanced osseous development. The voice is frequently deep, and on the skin are seen acne efflorescences, as is often seen at the age of puberty. The cholesterol content of the blood is in some cases considerably increased, in others it remains low. Hypertension is frequently found.

In these cases excretion of both estrogen and androgen is as a rule found to be greatly increased (Gross, Frank). This, however, is not conclusive, as cortical neoplasms without estrogen excretion have been recorded, and the clinical picture of cortical tumors is on the whole strongly varying. Thus the virilizing effect may be absent, and the disease may present a picture resembling that of the pituitary basophilism with plethoric habitus, full-moon-face, obesity, hypertension, atrophic cutaneous striae etc. What chiefly concerns us here, however, is that these tumors in a few cases may exert a feminizing action. CASIDA & HELLBAUM have shown experimentally that injections

of adrenal extract from mares and geldings may give rise to follicular menstruation and ovulation in rats, and Pottinger & Simonsen have prepared, from Swingle & Pfiffner's adrenal extract, one fraction which caused atrophy of the uterus in female rats, growth of testes and increased spermiogenesis in male rats, and another fraction producing the opposite effect. There are very few clinical cases confirming this, however. Male cases of gynecomastia, even with lactation, have been reported as a consequence of adrenal tumor, but only 6 in all, and the younges of these was 15 years old (Lisser reports 1 case and refers to cases, Simonsen & Joll report 1 case). Thus the condition must be extremely rare in children. That adrenal tumors may also produce feminine pubertas praecox is seen from a peculiar case reported by Walthers, Wilder & Kepler.

A previously healthy girl, age 4 years, started growth of the breasts and hypertrichosis, her voice becoming coarse and deep. When she was 8 years old, menstruation occurred which lasted 4 days, and later she had very sparse menstrual bleedings at intervals of 2 months. When she was 9 years old, she presented obesity, hypertrichosis both in the face and on the trunk, particularly on the mons veneris and in the armpits, striae atrophicae cutis, acne, hypertension, advanced osseous development corresponding to that of a 12 year old girl, and strong development of breasts and external genitals including clitoris. After a cortical adenoma had been removed by operation, the symptoms disappeared, the genitals, however, persisted to be of almost adult size, only the clitoris becoming distinctly smaller.

Even though this certainly exceptional case presents both menstruation and hypertrophy of the breasts, there are many of the typical adrenal symptoms, too, and a pure isosexual feminine pubertas praecox with regular menstruation and without clitoric hypertrophy has hardly been observed in cases of adrenal tumor.

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Cerebral affections, mostly tumors, but also encephalitis, hydrocephalus, and vascular disturbances, may cause pubertas praecox, though chiefly in boys. Wimmer has mentioned 1 boy, and Ford & Guild a boy and two girls with pubertas praecox after encephalitis, and Dorff & Shapiro have described 2 girls with pubertas praecox, without menstruation, as a consequence of hydrocephalus.

A tumor of the pineal gland is often mentioned as being responsble for the syndrome, but that is only part of the truth. The assumption that the pineal gland has some function in the development of puberty, cannot, as was emphasized particularly by Krabbe in 1923, be upheld, and subsequent investigations have discovered nothing to alter this view. Bing, Globus & Simon have collected 177 cases of tumor of the pineal gland, 21 of these showed pubertas praecox, only one in a girl. In that girl there was only slight manifestation of the syndrome, nor had she menstruated. Fifteen of the above 21 patients, moreover, presented typical hypothalamic symptoms (polydipsia, polyuria, polyphagia, somnolence, obesity etc.), and in eighteen of the patients, operation or autopsy revealed changes in the hypothalamus and the adjacent regions, or internal hydrocephalus. There is strong evidence, therefore, that the disturbance of growth in these cases is not primarily due to the tumor of the pineal gland, but on the contrary to the secondary lesions in the adjacent cerebral regions due to mechanical effect produced by this tumor.

Now it is just in these regions, i. e. round the posterior part of the third ventricle, that neoplasms causing pubertas praecox are most frequently found. Weinberger & Grant (in 1941) were able to collect 17 cases of tumor associated with pubertas praecox, 13 of which had this location. Only 3 of those 17 patients were girls. The tumor is most frequently made up of nerve tissue, and is described as neurofibroma, ganglioneuroma, astrocytoma, hamartoma etc., but craniopharyngiomas have likewise been found in cases with pubertas praecox. Often the tumor is small, growing slowly, and indistinctly marked off from the surrounding tissue. There are thus only few features left to associate it with the usual notion of a tumor, and it has the character of a malformation rather than a proper neoplasm.

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The typical symptoms noted in these cases are 1) precocious, isosexual maturation of the genitals with spermiogenesis, follicular maturation, ovulation and menstruation; 2) appearance of secondary sex characteristics; 3) strong somatic growth with advanced development of bone nuclei, and early fusion of the epiphyseal lines; 4) sometimes disturbances in the water balance; 5) lack

or minimal signs of an expanding lesion. Considering the location of the tumor, it is peculiar that very few cases show other vegetative hypothalamic symptoms than changes in the volume of the diuresis. Possibly the reason is that it is the posterior part of the hypothalamus which is chiefly involved.

As mentioned, only three such cases have been described in girls (until 1941).

The case reported by Gross was that of a girl, aged 1, who started strong development of the breasts, menstruation and increased bony growth. Other findings were oliguria and very slight unilateral reduction of strength but otherwise she presented no neurological symptoms. The hormone examination performed on different days disclosed an excretion of 405, 324, 648, 36, 175, 270, and 12 M. U. of estrogen, gonadotropic substance, apart from a single doubtful reaction, not being found.

Exploratory laparotomy disclosed some enlargement of uterus and ovaries, mature graafian follicles but no tumor. Encephalography having revealed dilated ventricles, craniotomy was proceeded to, and death ensued 5 days later. Autopsy revealed a tumor measuring 4.5 cm in length and 3—4 cm in width, originating from the floor of the third ventricle and mamillary bodies.

Histologically the tumor was classified as a hamartoma, *i.e.* a neoplasm poor in cells, chiefly made up of glia cells and glia fibers, indistinctly separated from the surrounding tissue, and without signs of active or invasive growth.

The other case (Bailey et al.) was that of a girl, 9 years old, with mature figure, large breasts and dense pubes, but without menstruation. A craniopharyngioma filling the third ventricle and interpeduncular fossa and compressing the pituitary body was found.

The third case (Clark et al.) was that of a girl who had had regular menstruation since the age of 6 months. At the age of 4 years she presented all the bodily characteristics of a mature woman, and measured 23 cm above normal height. Here, too, an exploratory laparotomi was performed with biopsy of the ovaries, which showed mature follicles and corpora lutea. She died, 6 years old, of a streptococcus infection, and autopsy disclosed a tumor in the interpeduncular fossa, the mamillary bodies and the floor of the third ventricle.

The first and the last cases are of interest because they show very early onset of pure isosexual pubertas praecox without, or with minimal signs of, brain lesion, and because death in neither case was directly due to this disease.

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It is in conformity with the above clinical observations that experiments in animals have shown that the posterior region of the hypothalamus is the seat of centres controlling estral behaviour and mating, and that ovulation can be provoked by direct stimulation of this region.

It is furthermore a fact that pubertas praecox can be produced experimentally in both animals and humans by injection of pituitary extract. It is a point of some significance, therefore, that tumors of the pituitary body is never found to be accompanied by pubertas praecox.

There is, accordingly, reason to believe that the hypothalamus contains centres which exercise a controlling and governing influence over the development and function of the sex organs and sex characteristics, and in the cases here dealt with, it must be supposed 1) that the abnormal development is due to an increased production of gonadotropic hormone in the pituitary body and 2) that the increased production develops because a tumor in the hypothalamus partly destroys the mechanism or nerve paths which under normal conditions control the pituitary production of these hormones.

However, this subject surely is a very complicated one, and it seems as if functions of other endocrine glands besides the gonads and the pituitary body may be affected, too. Thus cases have been observed of simultaneous occurrence of tumors of the pineal gland and the adrenal glands, and Hooft et al. have described a case of isosexual pubertas praecox in a girl 2 years old of 'herculean build' with cholesteremia and hyperglycaemia suggesting increased adrenal function. Autopsy disclosed a tumor of the left mamillary body.

In this connection may be mentioned some peculiar and very rare cases of osteodystrophia fibrosa associated with pronounced pubertas praecox, pigmentation of the skin, and hyperthyreoidism, only occurring in girls. Such cases are reported by Albright and McCune & Bruck.

There are, however, several cases of pubertas praecox in which it is impossible clinically to demonstrate other morbid symptoms, or any cause of the early development, and which have therefore been termed constitutional, essential, or genuine pubertas praecox. If the afore-mentioned case (Clark et al.) is borne in mind, in which the tumor diagnosis was made only because the child died of an incidental streptococcus infection, the uncertainty of the clinical definition of this class is readily understood. These cases have, however, one very essential and characteristic feature in common, which justifies this grouping, and to which it is due that the condition is called an abnormity rather than a disease, and that is the circumstance that the children, except for their abnormal development, thrive as normal individuals, without morbid symptoms and with normal duration of life. Probably that accounts for the absence of autopsy reports.

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The abnormality develops very early, commencing with enlargement of the breasts, and menstruation, often during the first year of life. Growth is very much accelerated, and the child soon aquires the appearance of a small well-proportioned, fully developed woman. The rapid growth stops, however, at the age of 10 or 11 years, and such 'giant children' become short as adults.

As a rule, their intelligence is normal, corresponding to their age, but their psychic development is frequently influenced by the precocious sexual development, some children being aggressive upon the other sex, whereas others are shy, coy and bashful.

Such cases are rare, however, and but few have been fully described. Bennet mentions a girl, aged 4 years, who menstruated after the age of 4 months. She was strongly attracted by men, 'she crawled all over men when given a chance'. Meigs reports the case of a girl who started regular menstruation at the age of 18 months, and whose health, at the age of 10, was satisfactory in every respect. Keating's child menstruated regularly from the age of 1 month; when she was 3 ½ year old, a follicular cyst the size of a nut was removed from one of her ovaries. The ovaries presented numerous scars after ruptured follicles. Her condition did not change after operation.

UDDENBERG mentions a girl from Gothenburg, in whom development of the breasts began when she was 3 ½ year old, and menstruation twelve months later. That child presented

hypotonia of the musculature of the extremities, but otherwise no neurological symptoms, and UDDENBERG discusses whether the condition may be due to 'Sjøbrink's encephalitis', a benign, insidious encephalitis of slow course, which is frequently associated with hypotonia and hormonal changes.

FEYDIT gives an excellent description of a girl who menstruated regularly since the age of 15 months and who, at the age of $3^{1/2}$ year, measured 120 cm and looked like a fully developed little woman.

Novak is of the opinion that this type, which he designates 'constitutional', is the most common type of pubertas praecox, although it hitherto has attracted least attention in the literature. He mentions 9 cases ranging in age from 15 months to 10 years. Six of these children were submitted to exploratory laparotomy, and one of them to ventriculography, without anything abnormal being revealed except ovaries with mature follieles and corpora lutea.

NOVAK agrees with FEYDIT in that the 'child-mothers' who are sometimes mentioned as freaks in the older literature, belong to this type. Thus there exists a report from 1658 of a 6 yearold mother (Manderlo). The youngest mother is reported to be a Peruvian girl who bore a child at the age of 5 years and 8 months. Feydit mentions 2 girls who menstruated at the age of 1 and 4, and were pregnant when they were 9 and 8 years old, respectively. That this early sexual development entails neither a shorter duration of life nor an early menopause, is evident from a report of a woman, aged 53, who, since the age of 2 1/2 year, had had regular menstruation, only interrupted by ten normal pregnancies, the first when she was 17 years old; she was still in perfectly good health with regular menstruation. Another woman, who menstruated since her 2nd year, and gave birth to a full-term still-born child when she was 8 years old, died at the age of 63.

In such children, of whom it has been pertinently said that 'they skip childhood', one would anticipate an increased estrogen excretion as compared with normal excretion at their age. Bennet thus found 5—7 M.U., UDDENBERG 20—30—20 M.U.,

FEYDIT 5 M. U., and NOVAK, in 4 cases, estrogen excretions from less than 3 to 40 M.U. UDDENBERG at the same time found excretions of gonadotropic homone of 80—40—40 units per litre, and FEYDIT found 20 units.

The changes giving rise to this abnormity presumably have their seat in the posterior part of the hypothalamus. The existence in this region of small, tumor-like, benign formations of the same nature as those mentioned in the verified cases of tumor, cannot be precluded. However, as no perceptible change in the structure of these parts of the brain occurs at normal puberty, it is not impossible that these cases of pubertas praecox are not accompanied by anatomical changes, but merely by such functional changes as occur at normal puberty. Puberty may be advanced or retarded by abnormal function of the endocrine organs, but normally the time for its occurrence must be fixed in the genetic constitution of the individual. In the above cases of pubertas praecox there must be a radical change in the chromosomal genetic mechanism. Therefore, Novak applies the term 'constitutional' to this type.

As mentioned before, the child here dealt with looks like a fully developed and harmoniously shaped girl at the age of puberty; although she is no more than 3 years old, her stature is that of a 5 year-old girl, and her bone development equal to that of a child 10 years of age.

The absence of a palpable ovarian tumor and of typical hormonal excretion in spite of nearly 4 years' standing of the anomaly, presumably excludes an ovarian tumor being responsible for the condition, and the purely feminine character, without hypertension, acne and increased hormonal excretion, likewise excludes the existence of an adrenal tumor. It is therefore to be assumed that some modification of the hypothalamic function is the cause of the child's condition.

Whether, then, the cause is a neoplasm or some other anatomical change, or whether the condition is due to a constitutional factor, it is difficult to decide. In most respects the case resembles the constitutional type, but on the other hand she presents some few and slight symptoms, which, despite the

oculist's and the neurologist's findings, arouse the suspicion that not only the hypothalamic functions regulating sexual and somatic development are influenced, but also that anatomical changes exert an action on other functions. These symptoms are a slight unilateral hypoplasia of the face, a periodical slight unsteadiness in the coordination of the eyes, a rather small daily urinary output, and the somewhat peculiar, hollow-eyed expression of the face.

In order possibly to get nearer the solution of the question, encephalography may be resorted to. However, even in case such an examination should disclose pathological conditions, it may not occation a change in the treatment, for the risk of surgical intervention in this region is so great that it will hardly be proceeded to as long as there is no vital indication for it. Unless fresh symptoms appear, causal treatment will have to be avoided, whereas endeavour will have to be made to help the child through the difficult time until she reaches the normal age of puberty.

The psychic and social difficulties certainly will be considerable. As previously mentioned, the psychic habitus of such children often bears the empress of their anomaly, some of them being sexually aggressive, a condition which naturally is dangerous in a child whose somatic development is that of an adult, but whose psychic development and experience, although being good for her age, does not correspond to her appearance at all. For this child, whose behaviour is characterized by shyness and reserve, this danger is scarcely very great at present.

However, not only in the sexual domain may this disproportion between bodily and psychic development imply danger, for the child will almost constantly be faced with difficulties with which she cannot cope, and this fact, combined with the consciousness of the difference between herself and other children will easily give rise to severe psychic conflicts during school-days.

This girl, fortunately, has a home which is capable of lending her adequate protection and guidance through the difficult and trying years until the other children of her age catch up with her, and one can only hope that she will be able, when grown up, to lead a normal life in spite of having had no normal childhood.

Summary.

Report of a case of feminine pubertas praecox: at the age of 7 months the child started growth of the breasts and pubes, and ever since she has menstruated regularly. When she was 3 ½ year old, she measured 108 cm, and her bone development was equivalent to that of a 10 year-old child. She looks like a small girl at puberty. After a discussion of the different types of feminine pubertas praecox, it is assumed that the child belongs to the so-called constitutional type, though the presence of anatomical changes of probably benign nature in the hypothalamus cannot be precluded.

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A Peculiar Case of Renal Insufficiency Simulating Diabetes Insipidus.¹

By

HOLGER DYGGVE and TAGE SAMSØE-JENSEN.

In the spring of 1946 a patient was admitted to the Pediatric Ward of the University Hospital who caused a number of diagnostic deliberations, and we have been unable to find any similar cases in the medical literature.

The patient, a boy aged $12^{1}/_{2}$ years, the son of a small holder in the country, was admitted under the diagnosis of diabetes insipidus and enuresis nocturna.

1st admission: From Feb. 5th to April 3rd 1946. Case book No. 129/46.

The patient's mother informed us that there are no hereditary disorders in the family, especially no cases of polyuria or polydipsia.

He is the eldest of 4 brothers and sisters, all of whom are in good health. Delivery, weight when born and his earliest development normal.

Of the ordinary diseases of childhood he has only had whooping cough and, apart from the disorder causing him to be admitted, he has always been in completely good health.

Already from the age of 2 or 3 years he has suffered from thirst and has been drinking far more than the normal, his diuresis having also been strikingly large. He was comparatively old when he did not wet himself in the course of the day, and he has always wetted his bed.

¹ Communicated at the meeting of the Dansk pædiatrisk Selskab (Danish Pediatric Society) on May 15th, 1946.

At the age of 7 to 8 years his thirst increased remarkably, his weight decreased much and he was inclined to feel cold. He was then admitted to the Kystsanatoriet (Coastal Sanatorium) at Nyborg, where he was staying for 6 months and where his weight increased a good deal. Still, his condition was unchanged after he had come home.

Since that time he has been drinking, on a rough estimate, 5 to 7 liters of fluid in the 24 hours, particularly in the morning he drinks greedily one liter of water. He wetted his bed several times every night and was unable to sleep, if he was not allowed to quench his thirst in the course of the night.

He has never had any febrile periods, visible hematuria, lumbar pain, oedemata, dysuria, headache or ocular symptoms.

The general practioner replied to our inquiry that no treatment of the disorder had been attempted, especially no treatment with preparations of the posterior lobe of the pituitary.

Objective examination: The patient is a small, lean but well-proportioned boy of a healthy appearance. Height: 130 cm, which is 15 cm less than the normal at that age. Weight: 27 kilos = the weight of his height. His carriage was poor, with marked scapulae alatae and a slight dorsal kyphosis.

The remaining objective examination showed nothing abnormal; especially the abdomen and the renal regions were natural. His psychical status was that of his age.

During his stay in this hospital the diuresis has varied from 3 to 4 liters, the maximum being 4.9 liters, and on a few occasions it was hardly 2 liters. The specific gravity varied from 1.001 to 1.006. To begin with he wetted his bed frequently, but he did not do so during the last period of his stay. He passed the water 10 to 12 times in the 24 hours, 4 or 5 times being during the night. The capacity of his bladder was impressively large, rarely below 300 cc., the maximum being 650 cc. As a rule he had a poor appetite, and, of course, he drank very much. For a couple of days we tried to restrict the fluid intake, but nevertheless the diuresis remained unchanged at 3 to 4 liters. Pituin powder for snuffing (*Medicinalco*) was administered ter in die

for 3 weeks without the slightest effect on diuresis and specific gravity.

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After that, the possibility that the patient suffered from diabetes insipidus was very doubtful. Although numerous examinations showed that the urine did not at any time contain protein or formed elements in microscopical examinations, the blood-pressure being normal too, a renal disorder had to be considered.

Laboratory examinations:

Hemoglobin: 83 to 86 %. Sedimentation test (micro): 13-1 mm/hour.

Mantoux (1 mg): negative. Wassermann's test: negative. AST': 80. Blood-pressure (numerous examinations): 110/60—90/60.

Serum calcium: 9.6 mg%. Serum phosphorus: 5.7—4.2 mg°... Plasma phosphatase: 89 U.

Serum bicarbonate: 18.8-20.0 m.-mol. Serum proteins 8.2% (alb.: 5.5%, glob.: 2.7%). Blood urea: 46-54-94-53 mg%. Urine: No albumen, sugar, blood or pus.

Microscopy of urine: nothing abnormal. Inoculation from catheter urine: no growth.

Sediment count a. m. Addis: normal figures (experience shows, however, that erythrocytes and cylinders are destroyed in highly diluted urine).

Examination of the eyes: Ophthalmoscopy and field of vision natural, astigmatismus hyp. invers.

X-raying of the skull, especially of the sella turcica: nothing abnormal.

X-raying of the thorax and epiphyseal lines: nothing abnormal.

Intravenous pyelography: only slight concentration of contrast medium, but from the excretion that is seen the calyces seem to be normal.

On cystoscopy with ureteral catheterization and subsequent direct pyelography completely normal conditions were found. No signs of hydronephrosis or dilatation of the ureters. The bladder is amazingly large.

¹ antistreptolysin titer.

Addis' concentration test showed a specific gravity of 1.004, but the result is uncertain, as the patient had not been thirsting for a sufficiently long period.

Urea clearance test was made twice, and showed 13.2 and 15.2 cc./min. respectively, i.e. an average decrease to 38.5 per cent. of the normal. Correction for the patient's surface, calculated to be 1 sq. m., was made.

Inulin clearance showed an average decrease to 11.7 cc./min., corresponding to 17 per cent. of the normal, which is 70 cc./min./sq. m.

Our diagnosis was then nephropathia (typus incertus), insufficientia renum.

The patient was dicharged but was re-admitted after the course of 1 month for control of the results of examination and verification of the diagnosis.

2nd admission: From May 1st to May 16th 1946. Case book No. 408/46.

The patient's condition is unchanged; he wakes, however, in the night when he has to pass the water. He feels quite well, attends school and assists in the field. He was somewhat catharral on admission; the objective examination showed nothing new.

This time the diuresis was about 5 liters (max. 6.1, min. 2.5), the specific gravity being 1.001 to 1.006. Insipidin (A.B.), $^{1}/_{2}$ ec. = 10 I.U., was administered in hypodermic injection, ter in die for 2 days without antidiuretic effect. In order to be sure that the preparation was really efficacious, we tried it on a healthy boy — with prompt effect after water rentention test.

Laboratory examinations:

In Addis' concentration test, where we succeeded in making the patient thirst for 24 hours, the specific gravity only increased to 1.009.

Microscopy of urine (10 days in succession): clear, acid or neutral, no proteins, no formed elements.

Inoculation from passed urine (3 times): no growth. Hemoglobin: 80 %. Blood-pressure: 110/70—100/55. Blood urea: 67—94 mg%.

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Serum calcium: 9.3—10.3 mg%. Serum phosphorus: 3.7—5.9 mg%. Serum bicarbonate: 20.3 m-mol.

Serum chlorine: 335 mg%. Urea chlorine: 80 mg%. After thirsting: Serum chlorine: 355 mg%. Urea chlorine: 120 mg%.

Takata's test: negative.

Serum proteins 8.6 % (alb.: 5.0 %, glob.: 3.6 %).

In order to obtain direct comparable values of the ultrafiltration, the back resorption in the tubuli, and the blood-stream through the kidneys, inulin clearance¹, urea- and perabrodif clearance¹ were made simultaneously on May 9th 1946. As only small plasma inulin concentrations were obtained in inulin clearance during the patient's first stay in hospital, the inulin was administered this time partially in intravenous injection, the concentration thus being increased to 30 to 40 mg%. The urea clearance was made in the hospital laboratory. At the same time analyses of urea solutions, unknown to the examiner, were made, a variation of 2 per cent. at the utmost being found. Unfortunately, the urea was not determined in plasma (like the inulin), but in heparin blood. The urea of plasma, however,

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Time	Diuresis per min. cc.	Plasma inu- lin mg%	Blood urea mg%	Urine inu- lin mg%	Urine urea mg%	Inulin	Urea	Perabrodil clearance	Curea	Cinulin	Clear, urea/ Cl. inulin
980-1004	3.9	29.6	54.1	130	257	17.2	18.5	86	4.8	4.4	1.08
1004-1034	2.8	38.8	58.6	178	275	10.6	10.9	63	4.7	4.6	1.03
1084-1100	4.5	40.1	56.9	174	243	19.5	19.4	106	4.3	4.3	0.90
1100-1145	4.9	41.2	59.0	194	239	23.2	19.8	118	4.0	4.7	0.85
1145-1230	3.5	42.9	53.0	227	227	18.5	14.7	92	4.3	5.8	0.80

At 830: 100 cc. of 10 % inulin hypoderm, and 15 cc. of 10 % inulin intravenously.

At 900: 4 cc. of 50 % perabrodil forte hypoderm. in the dilution 1: 4. The patient was asked to empty his bladder completely at the middle of each period. (In the second period the bladder did not seem to be completely evacuated.)

At 11° insipidin, 10 I.U., in deep hypodermic injection. No increase of the blood-pressure afterwards.

¹ The inulin and perabrodil clearance tests were made by Dr. Poul Kru-HOFFER and Dr. Flem. Raaschou, to whom our best thanks are due.

is only a few per cent. higher than that of full blood (Peters and VAN SLYKE (13)).

This time, too, a considerable reduction of the renal function was found (see the Table), and in the perabrodil clearance a reduction of the blood-stream through the kidneys was ascertained.

For the first three periods the Table shows an average inulin and urea clearance of 15.8 and 16.3 cc./min., which is 22.5 %, respectively 37.9 % of the normal. The perabrodil clearance shows a considerable decrease of the blood-stream through the kidneys, estimated at 33 per cent.

If, in our experiment, the ratio between the urea and inulin clearance values is considered, it will be seen almost to equal 1, which means that all the urea is excreted, which must be said to be favourable to the patient. The fact that the urea clearance is a little higher than the inulin clearance in a few periods must be due to experimental errors.

40 to 50 per cent. of the urea are considered to be subject to back resorption in normal diureses, and numerous investigators (among others BJERING (3)) find a fairly constant ratio between urea and creatinine clearance. The same applies to the urea and inulin clearance ratio (4). This parallelism is found both in healthy individuals and in patients suffering from nephritis, considerable individual variations from the normal value, however, being found in the latter. A considerable change of the ratio should be expected, whether the back resorption of the urea is active or passive owing to the often considerable pathologic-anatomical alterations found in the tubuli of patients suffering from renal disorders; but, as mentioned, this is most frequently not so. The displacement of the urea clearance which is seen in our patient, so that it is almost identical with the inulin clearance, is very remarkable and it does not seem to have been described previously.

The back resorption of the urea may be active or passive. Opinions about this question still seem to be highly differing. The adherents of the passive re-diffusion (Rehberg (16), Shannon (18), Brønnum Schou (17) et al.) have found increasing excre-

tion of urea with increasing diureses, as the high dilution reduces the possibilities of re-diffusion. This fact should thus explain the alteration of the above mentioned fairly constant ratio between the urea and the inulin (creatinine) clearance, as the urea clearance with increasing concentration index will approach the inulin clearance.

Adherents of the active back resorption (BJERING among others) believe that the importance of the diuresis to the excretion of urea no doubt is highly exaggerated. In a publication by BJERING (2) it is shown that pituin increases the retransfer of urea in the tubuli (this was shown by Poulson too (14)). This increased back resorption takes place independently of the alterations of the concentration index for creatinine, and this is why he does not consider it probable that a simple, passive re-diffusion takes place when the urea clearance decreases; but he supposes that the capacity of the tubulus cells for active back resorption is changed after injection of pituin.

We concluded our experiment with the administration of insipidin, 10 I.U. (the two last periods in the Table). We observed no distinct change of the concentration indices for urea and inulin, but the ratio between the urea and the inulin clearance shows a decrease, reflecting an increased retransfer of urea. This seems to support the theory of the active back resorption of urea in the tubuli. But, of course, too far reaching conclusions cannot be drawn from a single experiment with one patient.

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Epicrisis: This is thus the case of a boy, aged 12 years, who has suffered from polydipsia and polyuria since the age of 2 to 3 years, having been otherwise in completely good health. While the boy was in hospital his diuresis has been about 4 liters; the diuresis-inhibiting hormone produced no effect, but there was a greatly diminished renal function without increase of blood-pressure and with no abnormal findings in the urine or uremic symptoms.

Discussion: To begin with we termed the case diabetes insipidus spurius, but by this is generally understood polyuria determined by a primary polydipsia, such as it is seen in psychopaths and in persons who drink much habitually (Krarup and Hanssen (11) and Jarløv (10)). In these patients the renal function is normal, and for that reason our patient cannot be suffering from such a disorder.

Can he be said to suffer from a real diabetes insipidus then? It can be excluded with certainty, since a number of investigators (WINER (21), IVERSEN, JACOBSEN and BING (9), BANSI (1), HANSSEN (7)) in genuine diabetes indipidus have found normal inulin (or creatinine) clearance, reflecting a normal ultrafiltration, and also increased back resorption in the tubuli after administration of the hormone of the posterior lobe of the pituitary with subsequent decrease of the diuresis and concentration of the urine. In the medical literature (Forssmann (6)) rare cases of polyuria are described in which no effect of the hormone of the posterior lobe has been obtained and in which it has been considered to be due to a disorder of the hypothalamic centres. This theory is inconsistent with the modern view of diabetes insipidus and the effect of pituitrin on the isolated kidney (STAR-LING and VERNEY (19)). It does not seem as if renal functional tests, especially inulin clearance, have been made in these cases. There can be no doubt then that our patient suffers from a chronie renal insufficiency.

We did not in our examinations find any signs of cystic kidney or other congenital malformations of the urinary organs.

Although, in the course of 3 months' observation, we did not find any pathologic constituents of the urine or increased blood-pressure, the patient must be supposed to suffer from a chronic interstitial cirrhotic kidney (Longcope and Winkenwerder (12)), possibly caused by a pyelonephritis in his early boyhood (Raaschou (15)).

Chronic renal disorders during childhood sometimes give rise to renal rachitis and renal dwarfism (SVENSGAARD (20)), in which cases changes of the serum calcium and the serum phosphorus need not be present. In some cases polyuria up to 2 or 3 liters may be seen. The fact that our patient is somewhat small of stature may perhaps be associated with his renal disorder.

With regard to prognosis it is doubtless most probable that

the disorder will be slowly progressive, ending in death in uremia; but it cannot be excluded that the process has healed and the condition has become stationary.

We should like to thank Lecturer Jens Bing, M. D. for his valuable advice and guidance in the examination of our patient.

Summary.

The following findings were made in a boy, aged 12 years, who since the age of 2 to 3 years has suffered from excessive thirst and polyuria (at present 4 to 5 liters daily) and who was considered to be suffering from diabetes insipidus:

- No effect of the hormone of the posterior lobe of the pituitary body.
- Normal urine and normal blood-pressure, but increased blood urea and greatly decreased renal function.
- The urea clearance identical with the inulin clearance, which is a remarkable fact not previously described.
- 4) The views on the excretion of urea are mentioned.
- 5) On injection of insipidin results were found which are supposed to support the theory of the back passage of urea in the tubuli by means of active cellular activity.

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On the Occurrence of Palpable Spleens in Healthy Newborn Babies and Healthy Infants.

By

Y. ÅKERRÉN.

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In the pediatric literature it is often stated that an enlarged spleen — in clinical language practically equivalent to a palpable spleen — is always pathological. In the new-born such a finding gives rise in the first place to suspicions of lues, although enlargement of the spleen has also been observed with icterus neonatorum gravis, in septic conditions, etc. In infants after the new-born period a palpable spleen is usual in a number of different pathological conditions, e.g. anemia, exudative diathesis, in pasty and over-nourished children, in rachitis, in connection with acute infections, in tuberculosis, etc.

Several authors, inter alios, Lemež and Pollitzer and the present author (1939, 1942), have shown that in the new-born a physiological enlargement of the spleen is often provable. By means of systematic daily examinations during the whole of the first week of life, I found that the frequency of a positive spleen palpation finding in clinically healthy children exhibited a statistically verified maximum on the third day after birth. The frequency of positive palpation findings before and after the third day showed a steadily progressive increase or decrease respectively. In my paper published in 1942 I endeavoured to explain the mechanism of this transitory swelling of the spleen during the new-born period.

As far as I have been able to find, nothing is definitely known as to the occurrence of a palpable spleen in healthy infants after

the new-born period. In any case I have not succeeded in finding any systematic investigation of this matter in the literature.

Palpation of the spleen in infants is not very easy, and it calls for practice and accuracy. It must not be ignored that subjective factors may play a part. The series of investigations presented here are intended, on the one hand, to serve as a control for my earlier investigations as regards the new-born period, and on the other to give an idea of the frequency of positive spleen palpation findings in healthy infants above the new-born age, but less than 6 months old. This age-limit has been chosen as the number of anamnestically and clinically healthy children which I have had occasion to examine after the age of 6 months is so small that the series cannot be worked up statistically.

The new-born in the maternity hospital at Linköping were all examined by me personally. The examination comprised, not only the palpation of the spleen, but also a general examination of the child's condition and state of health. Attention was also paid to the course of the partus and to the mother's state of health. If there were any pathological features, the child in question was not included in the series presented here. The birth weight was not less than 2 900 g. Some of the infants had been admitted to a home for unmarried mothers, where, in my capacity as pediatrician, I supervised their condition. During the period to which the investigation refers, the children included in the series received either breast-milk only, or in the cases where they received »allaitement mixte», principally breast-milk. Some of the other children were from a small private infant welfare centre, where I controlled them regularly. The selection principles as regards feeding were the same here, too. In this series also the rule was observed, that only babies whose birth weight had exceeded 2 900 g were included. In all the cases careful attention was paid to the children's condition at the time of the examination, to their general state, the colour of the skin, behaviour, weight increase, and the state of the internal organs. Attention was also paid to the anamneses and the statements of the nurses regarding the care of the child and its condition between the control examinations. I have tried to exclude cases where any

obvious, even though slight, infection condition had been observed before the examination. When one and the same child had been examined several times and yielded different findings in respect of the spleen, consideration has been paid only to the result of the *first* examination.

Among the new-born in this series, each child was only examined once during the first week of life, in contradistinction to the procedure in my series published earlier. In the following table both the observations from the series presented here and from the older series published earlier, are collocated, to facilitate the comparison.

	1	2	3	4	5	6	7th day of life
New series	150	107	150	100	105	150	100
No. examined	158	137	158	162	165	150	130
Of which with palp- able spleens	42	49	72	64	50	38	25
Pos. palp. findings as % of no. examined	27.2±3.5	35.8±4.1	45.5±4.0	39.5±3.8	30.3 ± 3.6	25.3 ± 3.5	19.2±3.5
Earlier series							
No. examined	144	144	144	144	144	144	142
Of which with palp- able spleens	40	58	77	68	54	40	32
Pos. palp. findings as % of no. examined	27.8±3.7	40.3±5.7	53.5 ± 4.2	47.2±4.2	37.5±4.0	27.8±3.7	24.0±3.6
Difference between the percentage figures for the two se-							
ries	0.6 ± 5.1	4.5 ± 5.7	8.0±5.8	7.7±5.7	7.2±5.4	2.5 ± 5.1	4.8±5.0

The table shows satisfactory agreement between the results in the two series, and this is also true of the statistical control. In the new series is found the same even curve-like course, with a maximum on the third day and with rising frequency figures for the positive palpation findings before and falling frequency values after that time, which characterized the earlier series. In the latter, where each child was palpated every day during the first seven days of life, the average frequency of positive

findings for each of the seven days was 36.9 ± 4.1 %. In the new series the corresponding average value is 32.1 ± 1.4 %. The difference between these two values is 4.8 ± 4.3 %. Thus the statistical agreement is good.

I have divided the older infants into two groups, one for the ages under three months and one for the ages between three and six months. In the first group, which comprises 113 children, the spleen was palpable in 20 cases, i. e. in 17.7 ± 3.6 % of the cases. In 67 children between the ages of 3 and 6 months the spleen was palpable in 10 cases, i. e. in 14.9 ± 4.4 % of the cases. The difference in respect of the frequency of positive spleen palpation findings in healthy infants aged more than 7 days but less than three months, on the one hand, and healthy infants between the ages of three and six months, on the other, amounts to 2.8 \pm 5.7% in this series. From a statistical point of view there is thus good agreement between the frequency of pos. spleen palpation findings in these two age-groups.

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A comparison between the frequency values for the new-born period gives the following results: the difference between the average frequency of positive palpation findings in the new-born in this series, now published for the first time, and in healthy infants under the age of 3 months amounts to $14.4 \pm 3.9 \%$, between the first-mentioned and children of the age of 3 to 6 months with positive palpation findings it is 17.2 ± 4.6 %. The difference between the average frequency of positive palpation findings in the old series of new-born and the frequency of positive palpation findings in children who are less than 3 months old is 19.2 \pm 5.5 %. The difference between the first-mentioned and the frequency of positive palpation findings in children between the ages of 3 to 6 months is 22.0 + 6.0 %. If the frequency of positive palpation findings in children who are seven days old in the new series of new-born is compared with the frequency for children who are respectively younger and older than 3 months, the following differences are found: $1.5 \pm 4.8\%$ and 4.3± 5.4 %. The corresponding differences between the frequency of positive palpation findings on the seventh day of life in the old series and the positive palpation findings in children who are

respectively younger and older than 3 months is 6.3 \pm 5.1 % and 9.1 \pm 5.7 %.

Thus it proves that a statistically verified frequency difference exists between the average number of positive palpation findings during the new-born period (1st to 7th day of life) and the number of positive palpation findings in older healthy infants who are younger than 6 months. Thus the frequency of positive palpation findings is higher during the new-born period than later during the first 6 months of life. On the other hand, a comparison between the frequency of positive palpation findings on the seventh day of life alone and in infants after the new-born period, but before the age of 6 months, shows that, from a statistical point of view, there is good or satisfactory agreement. In other words — already on the seventh day of life the frequency of positive spleen palpation findings is approximately the same as later during the first six months of life.

It would have been of great interest to investigate in a larger series how often, in one and the same healthy infant examined at regular intervals, positive and negative palpation findings are found to succeed each other, for during the new-born period it not infrequently proves that, if the same child is examined daily as far as possible under similar conditions in respect of room temperature, time of day, interval which has elapsed from the immediately preceding meal, etc. - as was the case in the first series investigation — on one day a positive palpation finding can be made, and on the following or during the next few days a negative one, and later again a positive finding. In some few older, healthy infants also I was able to make similar observations, inasmuch as at one examination I made a positive finding, at another a negative one, and subsequently a positive one. This circumstance proves that in healthy infants constant fluctuations in the matter of the degree of fullness of the blood reservoirs of the spleen must probably be expected. As I pointed out earlier, the physiological swelling of the spleen in healthy new-born infants is a dynamic, not a static, phenomenon. Naturally this does not prevent the possibility, as POLLITZER suggested, of there being children with congenital »splenomegalia», on the one hand, and children with congenital »microsplenia», on the other. However, there is no investigation available which shows that such a constitutionally conditioned difference actually exists.

In my earlier works on physiological enlargement of the spleen in the new-born, I pointed out that the high frequency of positive palpation findings which is met with during the new-born period, and especially during the third day of life, is in all probability due to an accumulation of blood in the spleen. I have placed this accumulation of blood in connection with the transition from the intra-uterine hypoxemia to the extra-uterine optimal supply of oxygen. The blood of the new-born is characterized by a very high content of hemoglobin per unit of volume, and this will probably be functionally connected with the intra-uterine hypoxemia. After the beginning of lung respiration this high hemoglobin content is to some extent unnecessary functionally. Under such circumstances it readily suggests itself to assume that the body's blood reservoir organs, among which the spleen occupies a prominent place, will be made full use of during the new-born period. A support for the conception that enlargement of the spleen in the new-born is conditioned by an accumulation of blood is, inter alia, the varying degrees of palpability of the spleen in one and the same child during several consecutive days, which I have just mentioned. Further support is afforded by the results of repeated experiments with adrenalin injections in connection with which I was regularly able to demonstrate that a readily palpable spleen becomes impossible to palpate a short time after the injection.

In all probability similar dynamic conditions prevail in the spleen in many of the cases where it is palpable after the newborn period. Thus a palpable spleen in a healthy infant is probably often an expression of an accumulation of blood in its reservoirs at that time.

In the clinical examination of infants, both new-born and older, attention must be paid to these positive palpation findings in completely healthy children. To anyone who does not realize that, not infrequently, the spleen is clearly palpable even in a healthy infant, a positive spleen palpation finding may lead to

confusion and give rise to misleading diagnostic speculations. Often, however, this disturbing factor will probably be absent owing to the palpation of the spleen not being performed with sufficient care. Care, patience and practice are required to be able to establish whether a spleen is palpable with any degree of certainty. The less practised or less careful examiner will probably often fail to discover such a »physiologically» palpable spleen. The enlarged spleen found in unmistakeable pathological conditions is in general more bulky and of firmer consistency than that observed in the healthy new-born or in healthy infants. In healthy children the spleen does not as a rule extend farther than at most one or two centimetres below the costal arch, and that only with relatively deep inhalation. In my experience the deep, short inhalations often observed in little children who are struggling against tears or screams present particularly favourable conditions for palpating the spleen. On the other hand efforts must be made to avoid violent fits of crying during palpation. In that connection I have often observed how a spleen which previously could be clearly palpated, »disappeared» during the course of violent and persistent crying. During the new-born period, however, relatively large and, above all, fairly firm enlargements of the spleen are not unusual, so that they are often discovered even by the less practised or careful investigator. In these cases it is important to bear in mind the possibility of physiological enlargement of the spleen and not immediately to suspect lues. This has been pointed out earlier both by Pollitzer and by myself.

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Summary.

The author gives an account of experiences in further investigations into the occurrence of palpable spleens in healthy new-born infants and in healthy infants below the age of six months. The results were as follows:

1) 1 060 clinically healthy new-born infants, with birth weights of at least 2 900 g were each examined *once* during the first week of life to establish the occurrence of palpable spleens. The frequency of positive palpation findings shows an evenly rising ten-

dency up to and including the third day of life, after which it steadily declines step by step. The results agree very well, even when statistically analysed, with a series published earlier by the present author, in which all the children were subjected to daily examinations of the spleen during the first week of life. Both the investigations series thus show that the frequency of positive spleen palpation findings exhibits a statistically verified maximum on the third day after birth. The average frequency of positive palpation findings in the new series is $32.1 \pm 1.4 \%$, the maximal frequency on the third day of life is $45.5 \pm 4.0 \%$.

- 2) Healthy infants, above the new-born age, show a frequency of positive spleen palpation findings which in the case of children younger than three months is 17.7 ± 3.6 % and for children between three and six months is 14.9 ± 4.4 %. The former series comprises 113 children, the latter 67. Statistically there is good agreement between the frequency of positive spleen palpation findings in healthy infants below the age of three months and that in children between three and six months of age.
- 3) There is a statistically verified difference between the average frequency of positive spleen palpation findings in healthy new-born infants, on the one hand, and in infants at ages between the new-born period and six months, on the other. Thus in healthy new-born infants a positive spleen palpation finding is considerably more usual than in other infants below the age of six months.
- 4) The author emphasizes the necessity of care and practice in spleen palpation on infant children. Further, the dynamic conditions which characterize the physiological enlargement of the spleen are emphasized. The enlarged spleen found in the case of pathological conditions in the new-born and in healthy infants is often more voluminous and of firmer consistency and therefore easier to observe than in the clinically healthy in the same agegroup. Nevertheless in infants which are entirely free from any signs of disease there is not infrequently a relatively large and firm palpable spleen. This is true particularly of the new-born period.

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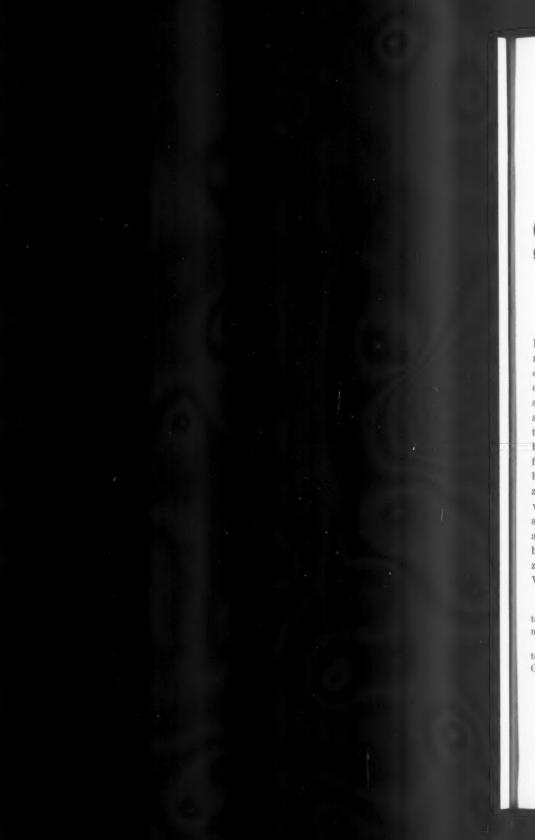
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Über zwei bei Säuglingen vorgekommene, in kurzer Zeit geheilte Fälle von akuter Hepatomegalie ohne Ikterus.

Von

N. HALLMAN.

Es ist allgemein bekannt, dass sich die Leber neben der Milz bei Infektionskrankheiten oft im Kindesalter sogar verhältnismässig beträchtlich vergrössert, um dann schnell nach Heilung der Infektion wieder kleiner zu werden. Selten ist es jedoch, dass die Grösse der Leber so gewaltige Ausmasse annimmt, dass sie fast ganz das Krankheitsbild beherrscht ohne klinisch feststellbaren Ikterus. Entsprechende Fälle sind in der Kinderabteilung des Allgemeinen Krankenhauses in Helsinki früher nicht behandelt worden. Nach unserer Ansicht und unseren Erfahrungen waren wir geneigt die Prognose der beiden Patienten beim Eintreffen im Krankenhaus als ausserordentlich schlecht zu betrachten. Die beiden Fälle heilten jedoch in kurzer Zeit vollständig. Da es uns nicht gelungen ist, in der Literatur entsprechende Beschreibungen zu finden, dürfte ihre Veröffentlichung am Platze sein, dessenungeachtet, dass die Untersuchungen, besonders was die Funktion der Leber betrifft, wegen des Kriegszustandes, währenddessen das Krankenhaus in bescheidenen Verhältnissen tätig war, keineswegs vollständig sind.

Fall Nr. 1 (Jr. Nr. 535/1944): Patient: 1 Monat, 22 Tage alte Tochter eines Maschinemeisters. Am 25.8, 44 ins Krankenhaus aufgenommen.

Vater 37 Jahre, Mutter 29 Jahre alt. Familie der Eltern und die Eltern selbst soweit bekannt gesund. Das Kind ist das jüngste von vier Geschwistern, von welchen die übrigen ganz gesund sind.

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Befinden der Mutter während der Schwangerschaft gut. Die Geburtswehen begannen zwei Wochen später als berechnet war. Da die Geburt in drei Tagen nicht spontan vor sich ging, wurde Kaiserschnitt durchgeführt. (Auch die früheren Entbindungen dauerten länger als normalerweise, über 2 Tage, aber die Kinder wurden trotzdem spontan geboren. Die Mutter hat enges Becken.) Geburtsgewicht 3 500 g. Kind sofort nach der Geburt munter.

Muttermilch kam von Anfang an spärlich. Zusätzlich wurde Haferschleim-¹/₂-Milch verabreicht. Mahlzeiten anfangs mit Pausen von 4 Stunden, später, nachdem das Kind krank geworden war, jede zweite Stunde.

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Der Nabel heilte in normaler Weise gut.

Im Alter von zwei Wochen erschienen an der Haut allmählich Geschwüre, und zwar anfangs an den Schenkeln und am Bauch. Die Geschwüre verschwanden in einigen Tagen. Bald danach schwoll der Bauch in kurzer Zeit beträchtlich an. Gleichzeitig wurde das Kind unruhig, ass fast gar nichts und hatte offensichtlich empfindlichen Bauch. Die Temperatur war 39° per rectum. Zwei Tage lang kamen grünliche Erbrechungen vor. Stuhlgang normal. Harn dunkel. Die Temperatur schwankte zwei Wochen lang zwischen 38 und 39°. Der Appetit war äusserst schlecht. Das Kind bekam zweimal einen ca. 5 Min. dauernden Krampfanfall, einmal beim Baden und einmal im Bett. War ca. eine Woche vor der Einlieferung ins Krankenhaus fieberfrei. Der Appetit war weiterhin sehr schlecht, Erbrechungen kamen nicht vor. Die Stühle kamen dichter, ohne indessen diarrhöisch zu sein. Das Kind ist weiterhin unruhig gewesen und schlief schlecht. An der Haut des Rumpfes zeigten sich zeitweise kleine, an Nesselausschlag erinnernde Flecken, die in einigen Stunden erschienen und wieder verschwanden. Der Bauch war weiterhin gross und aufgebläht. - Husten war während der ganzen Zeit überhaupt nicht aufgetreten. Als Therapie wurde Regulierung der Nahrung und beruhigende Mittel angewandt. Da das Kind ständig schwach und krank ist, wird es ins Krankenhaus gebracht.

Status praesens: Der Patient sieht bleich und schwerkrank aus. Gewicht 3 280 g. Länge 55 cm. Kopfumfang 36 cm. Brustumfang 32,5 cm. Temperatur 36,2° per rectum. — Konstitution ziemlich schwach. Subkutanes Fettgewebe spärlich, reduziert. Haut und Schleimhäute blass, nicht ikterisch. Elastizität und Turgor der Haut herabgesetzt. Hinter dem rechten Ohr ein ca. kirschengrosser, fluktuierender Abszess. An der rechten Seite des Rumpfes Narben von Geschwüren. — Im Nacken einige erbsengrosse und in beiden Leistenbeugen einige bohnengrosse harte, unempfindliche, hinsichtlich ihrer Umgebung bewegliche Lymphknoten. — Muskeln schwach. Bewegungen schlapp. Brustkorb, Rückentrakturen.

Bewusstsein klar. Pupillen rund, gleichgross, reagieren auf Licht. Spannung der Fontanellen herabgesetzt. Keine Nackensteifheit. Reflexe normal. Sensibilität normal.

Atmung costa-abdominal. Atmungsfrequenz 40/Min. Lungen ohne Befund.

Herz auskultatorisch und perkutorisch ohne Befund.

Schleimhaut des Mundes ohne Befund. Bauch gebläht, Bauchdecken leicht gespannt, Meteorismus. Leber vergrößert, indem sie sich in der Mittellinie bis zum Nabel erstreckt. Links vom Nabel eine sich deutlich an die Leber anschließende, ca. hühnereigroße, fast bis zur Symphyse reichende Resistenz. Oberstäche der Leber glatt, ihre Konsistenz verhältnismäßig sest, keine nennenswerte Empfindlichkeit. — Milz nicht palpabel, ihre Dämpfung nicht vergrößert.

Harn: Farbe normal, klar, neutral. Alb. -, Nyl. -.

Faeces: Halbfest, grünlich, etwas schleimig, alkalisch. Weber: —. Wagner: —.

Pirquet: —, Mantoux (0,1 mg): —.

Blutbild: Hb. 54/68, Er. 2,92, I. 1,16, L. 18 500. Diff.: Neutr.: Myel. 0,5, jg. 0,5, st. 12,5, sg. 23,5. Eos. 1,5.

Bas. 0,5. Mon. 4,0. Ly. 57,5. Er. blast. 1/100.

Decursus morbi:

26.7. Die Resistenz hinter dem rechten Ohr wird incidiert.

31.7. Etwas Erbrechen. Zahlreiche Stühle, darin Schleim. In der Haut und in den Schleimhauten weiterhin keine Ikterischkeit. Konsistenz der Leber etwas erweicht.

2.8. In den beiden Leistenbeugen kleine Abscesse, aus welchen bei der Incision Eiter austritt. — Bauch nicht mehr so stark gebläht. Leber etwas kleiner geworden.

Blutbild: Hb. 54/68, Er. 3,14, I. 1,08, L. 25 700.

7.8. Blutbild: Hb. 53/66, Er. 2,82, I. 1,10, L. 15 400. Diff. Neutr.: Myel. 0,5, jg. 0, st. 9,5, sg. 46,0. Eos. 3,0.

Bas. 1,0. Mon. 2,0. Ly. 38,0. Er. blast. 0.

8.8. In den letzten Tagen ist die Leber schnell kleiner geworden. Sie ist jetzt nicht mehr unter dem rechten Rippenbogen fühlbar. Auch die links nach unten sich erstreckende Resistenz ist verschwunden. — Allgemeinfinden schlecht. In den letzten Tagen reichlich Stühle, welche dünnflüssig und schleimig waren. Gewicht hat abgenommen. Heute 2 880 g.

12.8. Allgemeinbefinden besser. Stühle seltener. Leber und Milz ohne Befund.

18.8. Blutbild: Hb. 63/78, Er. 3,78, I. 1,05, L. 11 050.

19.8. Allgemeinbefinden weiterhin besser. Stühle halbfest, nicht mehr schleimig.

23.8. Blutbild: Hb. 53/66, Er. 3,16, I. 1,04, L. 7 900.

28.8. Befinden gut. Verdauung in Ordnung. Gewicht steigt regelmässig. Leber ohne Befund.

1.9. Blutbild: Hb. 64/80, Er. 3,67, I. 1,26, L. 15 900.

16.9. Blutbild: Hb. 70/88, Er. 3,99, I. 1,10, L. 14 800.

 Wird aus dem Krankenhaus entlassen. Allgemeinbefinden gut. Gewicht 4 580 g. Leber und Milz nicht nachweisbar vergrössert.

Therapie: Nahrung bestehend aus Milchsuppe mit eingequirltem Ei, Zitronensäure-Milch und einem kleinen Teil Muttermilch. — Per os: Ascorbin und Leberpräparäte. Dreimal kleine Mengen Blut intravenös.

Nachfrage: (30.3. 45) Nach der Entlassung aus dem Krankenhaus ist das Befinden des Patienten sehr gut gewesen. Die geistige und körperliche Entwicklung wich in keiner Weise von den Altersgenossen ab.

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Kurze Zusammenfassung: Ein nicht ganz zwei Monate altes Kind bekommt im Alter von zwei Wochen am ganzen Körper Geschwüre. Bald danach konstatiert man eine bedeutende Temperaturanstieg, der Bauch schwillt an und wird hart sowie empfindlich. Eine Woche vor dem Eintreffen im Krankenhaus wird es fieberfrei. Allgemeinbefinden war weiterhin sehr schlecht. Im Krankenhaus wird Vergrösserung der Leber festgestellt. Sie erstreckt sich rechts und in der Mittellinie bis zur Höhe des Nabels. Links ist eine an die Leber anschliessende Resistenz fast bis zur Symphyse. Oberfläche der Leber ist glatt, hart, etwas empfindlich. Nach nahezu zwei Wochen wird die Leber soviel kleiner, dass sie nicht mehr fühlbar ist. Die Milz ist während der ganzen Zeit nicht nachweisbar vergrössert gewesen. Klinisch konnte kein Ikterus festgestellt werden. - Im Krankenhaus sind Stühle anfangs lose. Die am Anfang verhältnismässig starke Anämie und relativ reichliche Leukozytose heilen schnell, und das Kind wird aus dem Krankenhaus nach 2 Monaten als Rekonvaleszent entlassen. Allgemeinbefinden gut.

Diagnose: Septicaemia. Anaemia sec. Abscessus hepatis?

Fall Nr. 2 (Jr. Nr. 130/1945): Patient: 7 Monate, 6 Tage alte Tochter eines Schriftstellers. Am 13.1. 45 ins Krankenhaus aufgenommen.

Der Vater und seine Familie gesund. Die Mutter der Mutter sowie der Bruder des Vaters der Mutter haben Lungenschwindsucht gehabt. Bei der Mutter wurde vor 10 Jahren Lues festgestellt, die sachgemäss behandelt worden ist.

Einziges Kind. Schwangerschaft der Mutter normal. Geburt lang und schwer. Kind gut entwickelt, sofort nach der Geburt munter. Geburtsgewicht 3 400 g. — Das Kind hat sich gut entwickelt, war frisch und gesund. Sitzt schon durch ein Kissen gestützt. Bekam die unteren Zähne im Alter von 5 Monaten.

Bekam bis zum Alter von 4 Monate nur Muttermilch. Danach Flaschenmilch, Milchsuppe und Kartoffelbrei. — Wohnt in einem sonnigen Zimmer zusammen mit den Eltern. Ist viel im Freien gewesen.

Mit Ausnahme eines kleinen, ein paar Tage dauernden Schnupfens vor ungefähr einem Monat ist das Kind gesund gewesen. Zehn Tage vor dem Eintreffen im Krankenhaus wurde das Kind unruhig, schrie viel und hatte schlechten Appetit. Wenn man es anrührte, wirkte das Kind heiss. Als der Patient zur poliklinischen Behandlung gebracht wurde, wurde die Krankheit für eine gewöhnliche Influenza gehalten, und es wurden Antipyretika sowie Stimulanzen verordnet. Dessenungeachtet verschlechterte sich das Befinden des Kindes nach Ansicht der Eltern. Das Fieber schien zwar bisweilen zu sinken, stieg aber bald wieder von neuem. Das Kind magerte ab und wurde blass. Vor 4 Tagen wurde festgestellt, dass der Bauch anschwoll und hart wurde. Die Temperatur blieb jetzt zwischen 39—40°.

Der Stuhl hatte während der ganzen Zeit der Krankheit normale Konsistenz. Nur seine Farbe, wie auch die des Harns war dunkler als gewöhnlich. Hatte vor zwei Tagen zweimal Erbrechen, Speisereste, danach etwas Husten. — Die Hautfarbe ist nicht gelblich gewesen, die Lippen sind etwas bläulich geworden. — Wird wegen ständiger Verschlechterung des Zustands ins Krankenhaus gebracht.

Status praesens: Der Patient sieht schwerkrank aus. Gesichtsausdruck schmerzlich. Haltung und Bewegungen frei, unruhig. — Gewicht 7 370 g. Länge 67 cm. Kopfumfang 42 cm. Brustumfang 44 cm. Temperatur 36,6° per rectum. — Körperbau schwächlich. Subkutanes Gewebe ziemlich spärlich, etwas reduziert. Haut und Schleimhäute blass, nicht im geringsten ikterisch. Kein Hautausschlag. Tonus und Turgor der Haut etwas herabgesetzt. Brustkorb, Rückenmark und Gliedmassen fehlerlos. Weder Lähmungen noch Kontrakturen.

Bewusstsein klar. Pupillen rund, gleichgross, reagieren auf Licht. Patellarreflexe ziemlich lebhaft, nicht multipel. Bauch- und Cremasterreflexe normal. Lasseque: —.

Atmung costal. Frequenz 30/Min. Lungen ohne Befund.

Herz auskultatorisch und perkutatorisch ohne Befund. Puls 150/Min.

Zunge feucht, nicht bedeckt. Im Munde unten zwei Zähne. Rachen ohne Befund. — Bauch gebläht, Bauchdecken weich. Leber stark vergrössert. Ihr Rand ist palpabel und erstreckt sich rechts von der Spina iliaca anterior superior nach oben geradlinig durch den Nabel, wonach er unter den linken Rippenbogen verläuft. Oberfläche und Rand der Leber glatt. Konsistenz fest, ist beim Palpieren etwas empfindlich. — Milz nicht nachweisbar vergrössert.

Harn: Farbe hellgelb, klar. Alb.: -. Nyl.: -.

Stuhl: Konsistenz normal, Farbe hellgelblich. Weber: —. Wagner: —.

Rtg. thorax: Herz und Lungen ohne Befund. Beide Sinus frei. Keine Zeichen von subphrenischem Abszess.

Rtg. Ventrikel (Kontrastmittel): Der Magen füllt sich gut. Ist stark nach unten und links geschoben. Entleerung in normaler Weise.

Pirquet: -. Mantoux (0,1 mg): -.

War: -, WaR Chol .: -, Kahn: -.

Blutbild: Hb. 31/39, Er. 1,56, I. 1,25, L. 42 300.

Diff.: Neutr.: Myel. 0, jg. 0,5, st. 6,5, sg. 43,0. Eos. 0,5.

Bas. 0. Mon. 4,0. Ly. 45,5. Er. blast. 1/100.

Decursus morbi: 14.1. Senkungsreaktion (Mikro) 35/46. — Temperatur über 38,5. Isst schlecht. Zweimal Erbrechen.

15.1. Blutkultur: Staphylococcus aureus.

18.1. Schwankende Temperatur. Allgemeinbefinden weiterhinschlecht. Kein Erbrechen mehr. Leber unverändert.

19.1. Blutbild: Hb. 29/36, Er. 1,61, I. 1,12, L. 10 000. Diff.: Neutr.: Myel. 1,5, jg. 2,5, st. 4,0, sg. 15,5. Eos. 1,5. Bas. 0,5. Mon. 3,5. Ly. 71,1. Er. blast. 15/100.

 Allgemeinbefinden etwas besser. Temperatur ad 39,9 gewesen. Lungen ohne Befund. Leber unverändert.

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Blutbild: Hb. 35/44, Er. 2,50, I. 0,88, L. 12 450. Diff.: Neutr.: Myel. 0, jg. 0, st. 13,0, sg. 28,5. Eos. 0,5. Bas. 0. Mon. 3,5. Ly. 54,5. Er. blast. 1/100.

25.1. Allgemeinbefinden bedeutend besser. Das Gewicht, das in den vorausgegangenen Tagen etwas zunahm, nimmt wieder ab. — Die Leberresistenz nicht verkleinert, dagegen etwas weicher geworden.

Blutbild: Hb. 55/68, Er. 3,57, I. 0,97, L. 7 200. Diff.: Neutr.: Myel. 0, jg. 0, st. 3,5, sg. 13,5. Eos. 0,5. Bas. 0,5. Mon. 4,0. Ly. 72,5. Er. blast. 0.

31.1. Allgemeinbefinden weiterhin gebessert. Ist 5 Tage lang fast fieberfrei gewesen. Gewicht hat immer noch abgenommen. Die Leberresistenz ist schnell kleiner geworden und erstreckt sich jetzt nur bis zwei Fingerbreit unterhalb des Rippenbogens. Während der ganzen Zeit liess sich nichts auf Ikterus Hinweissendes feststellen.

2.2. Senkungsreaktion (Mikro): 43/50. Blutbild: Hb. 60/75, Er. 4,25, I. 0,88, L. 11 700. Diff.: Neutr.: Myel. 0, jg. 0, st. 4,0, sg. 23,0. Eos. 5,0. Bas. 2,0. Mon. 2,0. Ly. 64,0. Er. blast. 0.

5.2. Allgemeinbefinden gut. Lungen und Herz o. b. Gewicht 6 820 g. Leber nicht mehr palpabel. Wird wegen Platzmangel nach Hause geschickt.

Therapie: Innerlich Sulfatiazol sowie Leber- und Eisenpräparate. Zweimal 100 ccm Zitratblut intravenös. 10.2. 45. Der Patient wird von neuem ins Krankenhaus gebracht, weil er am Abend vorher zu fiebern begann. In der Zwischenzeit ist das Kind gesund gewesen und hat gut gegessen. Bei der Untersuchung wird festgestellt, dass sich die Leber zwei Fingerbreit unterhalb des rechten Rippenbogens erstreckt. Ihre Oberfläche ist glatt, die Konsistenz verhältnismässig weich, keine Empfindlichkeit. Sonst nichts Pathologisches festzustellen. Senkungswert (Mikro) 43/47. Die Anzahl der roten Blutkörperchen hat etwas abgenommen. Leichte Leukozytose und Verschiebung nach links, die beide während des Aufenthalts im Krankenhaus abnehmen. — Der Patient wird am 19.2. 45 als völlig symptomfrei aus dem Krankenhaus entlassen.

Nachfrage: 28.3. 45. Der Patient hat sich während der ganzen Zeit sehr wohl gefühlt. Das Gewicht hat regelmässig zugenommen, und Bauchsymptome sind nicht aufgetreten. Senkungswert 24/1 St. Über das

Blutbild nichts Besonderes.

Kurze Zusammenfassung: Ein 7 Monate altes Kind bekommt plötzlich Fieber. Am Anfang ist nichts Besonderes festzustellen, aber 10 Tage später bei der Aufnahme in die Klinik wird konstatiert, dass die Leber sich gewaltig vergrössert hat. Die Mutter hat beobachtet, dass der Bauch schon 4 Tage vorher anschwoll. Die Leber erstreckt sich von rechts von der Spina iliaca ant. sup. an über den Nabel unter den linken Rippenbogen. Die Oberfläche ist glatt, die Konsistenz hart, und beim Palpieren zeigt sich etwas Empfindlichkeit. Die Bauchdecken sind nicht gespannt. Im Röntgenbild wird festgestellt, dass der Magen stark nach links verschoben ist, worauf die in den letzten Tagen vorgekommenen Erbrechungen offenbar zurückzuführen sind. Die Milz ist nicht nachweisbar vergrössert. Ikterus ist klinisch nicht festzustellen. Aus dem Blut entwickelt sich der Staphylococcus aureus. Starke Anämie und Leukozytose. Das äusserst schlechte Allgemeinbefinden hebt sich in ca. einer Woche. Nach nahezu 3 Wochen wird der Patient als Rekonvaleszent aus dem Krankenhaus entlassen. Leber ist jetzt nicht mehr palpabel. Senkungsreaktion (Mikro): 43/50. Im Blutbild nichts Besonderes. Nach nicht ganz einer Woche bekommt der Patient von neuem Fieber. Auch diesmal ist die Leber etwas vergrössert, aber die Besserung geht schnell vor sich. Der Nachfrage gemäss geht es dem Patienten gut.

Diagnose: Septicaemia cum hepatomegaliam. Anaemia secundaria.

Diskussion:

Beide in Frage stehenden Kinder sind im Säuglingsalter. Das erstere erkrankte schon einige Wochen nach der Geburt, und die Krankheit war bei der Einlieferung in die Klinik schon weit vorgeschritten. Der letzteren Fall ist insofern sehr klar und aufschlussreich, als wir Gelegenheit hatten, die Entwicklung der Krankheit ganz vom Anfangsstadium an zu verfolgen. Zehn Tage vor der Aufnahme in das Krankenhaus war das Kind untersucht worden, und ausser dem Fieber war nichts Besonderes festzustellen, so dass die Krankheit zunächst für ein gewöhnliches Influenza-Fieber gehalten wurde. Die Vergrösserung der Leber ging nachweisbar im Verlauf kurzer Zeit vor sich. Offensichtlich verhielt es sich bei dem ersteren Fall genau so, aber bei diesem mussten wir uns nur auf anamnestische Angaben verlassen. In beiden Fällen wurde die Leber in kurzer Zeit wieder kleiner.

Im letzteren Fall wurde die Blutkultur durchgeführt, wobei sich der Staphylococcus aureus entwickelte, was zeigte, dass es sich um Septikämie handelte. Im ersteren sind in der Anamnese das typische Fiebern und die während längerer Zeit am ganzen Körper auftretenden Eiterherde an der Haut ein deutlicher Beweis für den gleichen Umstand. Beim Eintreffen im Krankenhaus bestand zwar kein Fieber mehr, aber vielleicht war der Organismus wegen des schlechten Allgemeinbefindens nicht mehr imstande, so zu reagieren.

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Gemeinsam für beide Krankheitsbilder ist fernerhin das äusserst schlechte Allgemeinbefinden sowie die relativ starke Anämie, die sich besonders bei dem letzteren Fall in kurzer Zeit entwickelt hatte und auch bedeutend deutlicher war als bei dem ersteren. Sowohl die Anämie als die besonders bei dem letzteren reichliche Leukozytose heilten desgleichen sehr schnell mit der Hebung des Allgemeinbefindens. Die wichtigste Ursache für die Anämie ist offensichtlich in der starken Infektion zu suchen.

Worauf beruht die starke Vergrösserung der Leber?

1. Am ehesten dürfte es sich um eine von der allgemeinen Septikämie verursachte Schädigung des Leberparenchyms handeln. Das schnelle Wachsen und die rasche Verkleinerung der Leber weisen vielleicht in erster Linie auf eine entzündliche Zellenund Flüssigkeitsansammlung hin. Wenn wir eine so gewaltige
Vergrösserung der Leber wie in diesen Fällen berücksichtigen,
würde es indessen natürlich wirken, dass die Funktion der Leber beträchtlich gestört wäre. Nähere Funktions-Untersuchungen
sind zwar nicht durchgeführt worden, aber der vollständig fehlende Ikterus ist jedenfalls ein merkwürdiger Umstand. Aus der
Anämie zu schliessen, ist Zerstörung der roten Blutkörperchen
indessen in grossem Ausmasse vor sich gegangen. — Merkwürdig
ist auch, dass gleichzeitig keine Vergrösserung der Milz festzustellen war.

- 2. Wenigstens theoretisch liesse sich denken, dass das starke Toxin das Knochenmark in solchem Masse geschädigt hat, dass der Organismus zur Neubildung des Bluts andere Organe mobilisieren musste, und dann zunächst solche, welche diese Aufgabe schon früher im fötalen Stadium gehabt haben, wie die Leber. Dies konnte wenigstens zum Teil zur Vergrösserung der Leber beitragen.
- 3. Es ist allgemein bekannt, dass im Zusammenhang mit Pyämien Leberabszesse auftreten können. Etwas derartiges konnten wir in diesen Fällen jedoch wenigstens nicht lokalisieren. Im Gegenteil ist die Leber diffus vergrössert und durchweg gleich hart gewesen. Ikterus trat desgleichen nicht auf. Die Resistenz links unten im Bauch bei dem ersteren Falle liesse sich zwar als etwas derartiges denken, aber so schnelle Heilung eines recht grossen Abzesses wirkt nicht glaubhaft. Dagegen könnte man sich denken, dass in der Leber mehrere kleine Herde gewesen wären. Das Fehlen des Ikterus und die schnelle Heilung der Krankheit wirkt jedoch auch dann sehr merkwürdig.
- 4. Gegen eine auf Herzinsuffizienz beruhende Stauungsleber spricht das Fehlen aller anderer Insuffizienz-Symptome. Stase-Rasseln in den Lungen, Beklemmung, Ascites oder Ödem traten in keinen von den beiden Fällen auf. Auskultatorisch und perkutorisch ebensowenig wie durch Observation des Pulses war nichts Unnormales wahrzunehmen. Im letzteren Fall wurde auch die Röntgenuntersuchung durchgeführt, ohne dass irgendwelche Hypertrophie festgestellt wurde, in welcher Weise das

Herz des jungen Kindes bekanntlich verhältnismässig schnell reagiert. Der fehlende Ikterus ist auch kein Beweis für die Stauungsleber.

Obwohl in diesen Fällen die Ursache für die Vergrösserung der Leber endgültig ungeklärt geblieben ist, sind diese klinischen Krankheitsbilder als solche sehr interessant. Gewaltige Lebervergrösserung während Pyämien, welche in kurzer Zeit trotz des schlechten Allgemeinbefindens der Patienten heilen, und während deren klinisch kein Ikterus festgestellt werden kann, sind sehr selten.

C

Etiological Studies on Malignant Epidemic Gastro-enteritis in Infants.²

By

K. BIERING-SØRENSEN, H. E. KNIPSCHILDT, H. VON MAGNUS and SV. TULINIUS.

The malignant epidemic form of gastro-enteritis that has prevailed in numerous pediatrics and maternity hospitals in the Anglo-Saxon countries — designated as *epidemic diarrhea of the newborn* — appears not to have been observed in Scandinavian countries until recently. Hitherto, thus, only a few small epidemics have been reported from Sweden (Selander, 1943; v. Sydow, 1945).

Since December 1943, however, several epidemics, in part mutually connected, have been observed among infants in various children's homes and pediatric clinics in Copenhagen. The disease has attacked in particular children under 3 months of age, especially premature or otherwise relatively weak infants. Unquestionable instances of this lesion have been observed, however, even up to the age of 9 months. Small epidemics have occurred also in several of the maternity clinics in this town.

From the present literature it appears as if the disease here observed has been of the same nature, clinically and epidemio-

¹ The present material has been gathered from the pediatrical clinics in Copenhagen: the Blegdam Hospital, Fuglebakken Children's Hospital, Queen Louise's Children's Hospital, Mrs. Hermansen's Clinik, Pediatric Deps. of the Northern Hospital, Rigshospital, St. Joseph's Hospital and Sundby Hospital.

² The work here reported was carried out with the aid of a grant from Kong Chr. d. X's Fond,

logically, as *epidemic diarrhea of the newborn*. The incubation period appears to be about 3—5 days and generally the lethality has been high. Of the ca. 500 cases recorded in Copenhagen and surroundings within the last two years over one-half terminated fatally.

Here in Denmark so far, the disease appears not to have occurred outside Copenhagen and surroundings. Lately the epidemics appear to have been of a somewhat less malignant character than previously.

As in *epidemic diarrhea of the newborn*, in the present cases autopsy has revealed practically no characteristic pathological changes apart from parenchymatous degeneration of the organs. In several of these cases, however, encephalitic changes have been found in the brain (ERNA CHRISTENSEN & BIERING-SØRENSEN, 1946, in press).

In spite of many careful investigations it has not been possible so far to demonstrate an etiology common to the serious epidemics of cholerine that have been raging previously and now again in recent years in most countries in Europe as well as in America.

Only in relatively few cases has it been practicable to demonstrate the presence of pathogenic bacteria of the Salmonella or dysentery group in the stools. Cooper and collaborators, who state they have found these bacteria in up to 50 % of the cases of gastro-enteritis in children admit themselves that the diarrheas in the first year of life — i.e., at the cholerine age proper — generally are not due to these bacteria. From a material compiled in this country, Bloch (1921) found »pathogenic intestinal bacteria» only in 10 % of the infants examined.

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Naturally, therefore, attention has been paid to other bacterial species isolated from the stools of the children affected, and gradually nearly all the bacteria occurring in the intestinal canal have been suspected as the cause of the various epidemics. The difficulty in deciding on the etiological significance of these bacteria is obvious, however, as the requirement concerning their obligate pathogenicity has to be left out of consideration, and no supporting evidence is to be obtained from animal experiments.

Ever since Escherich's classical works on the bacterial flora

in the stools of infants, it has been known that the intestinal flora in breast-fed infants chiefly is made up of lactic acid-producing bacteria, especially of the bifidus and acidophilus-group, as well as enterococci and coli (cf. Mejlbo, Nygart & Plum, 1941).

At the least sign of dyspepsia or on changing the diet to cow's milk this condition is altered through the appearance of other bacterial species. In dyspeptic stools the bacterial flora becomes even more polymorphous through the appearance of a varying number of mostly proteolytic bacteria.

Originally Escherich thought that in Bact. coli commune he had found the cause of most cases of cholerine. But, naturally this idea had to be given up again when colon bacteria were found also to be present in most children without any intestinal affection. After Bahr & Thomsen had demonstrated the significance of various colon and metacolon bacteria in the development of some cases of cholerine, it seemed obvious to assume that cholorine was due to specific coliform strains transmitted from one patient to another or possibly to an increase in the virulence of such bacteria in the intestinal canal of the patient, resulting from a temporary decrease in the resistance of the organism (Escherich, Bloch).

In a series of papers Bessau and collaborators have further elaborated this theory concerning the pathogenetic significance of the colon bacillus in the incidence of cholerine in infants (Bessau & Bossert, 1919; Bessau, 1933).

Through systematic studies on the fermentative aspects of coliform bacteria, Adam was able to identify some specific colon strains (*dyspepsicoli*) found in the feces from most of the children with serious gastro-enteritis, while such strains were found but very seldom in the feces of normal infants, and never in adults. On the basis of these findings he took the infantile intoxication to be due to an infectious enteritis produced by the *dyspepsicoli* demonstrated by him.

The results reported by ADAM have been confirmed by some authors (GOLDSCHMIDT 1933, KLEINSCHMIDT 1935). But most authors have been unable to demonstrate the presence of »dys-

pepsicoli» even with only a fair degree of regularity in cases of acute gastro-enteritis and dyspepsia (KYRKKI 1944, TAGAWA 1938, and several others).

Some authors found »dyspepsicoli» with the same frequency in the feces of normal children and sick children; and Denecke (1934) thought he was able to demonstrate that these colon strains are not more pathogenic than the ordinary colon strains.

BAHR (1935) reported that he had found a hemolytic colon strain to be the cause of an epidemic, whereas BRENNER & HARPER (1939) found only non-hemolytic colon strains in several cases of a very malignant form of gastro-enteritis.

In recent years LODENKÄMPER (1941) and KYRKKI (1944) have investigated the pathogenicity of many colon strains, and they both arrived at the conclusion that there are no »specifically pathogenic» strains.

In this country, in the State Serum Institute, extensive investigations have been carried out on the systematic aspects of the colon bacteria, elucidating especially the serological aspects of these bacteria (Kaufmann 1943—44, Knipschildt 1945). In these investigations it proved possible to divide the colon bacteria in groups and types on a serological basis.

As now it was practicable to classify more exactly a good many of the strains belonging to the colon group, we decided to try if we might be able in the stools from infants with malignant gastro-enteritis to demonstrate some particular serological groups that are encountered in the feces of normal infants but seldom or not at all.

Hitherto we have examined about 50 specimens of feces from infants with gastro-enteritis. In all of these cases the feces were found to contain colon bacteria belonging to a certain sero-logical group (group 26; see KNIPSCHILDT: »Undersøgelser over Coligruppens Serologi.» Dissert. Copenhagen 1945). In 7 cases the isolated strains belonged to another serological group (group 44).

For control, 35 specimens of feces from normal infants were examined in the same way. Group 26 was found not to be represented in any of the specimens, while group 44 could be de-

monstrated only in 2 cases. Neither type has ever been demonstrated in adults.

Group 44 was found chiefly in a certain gastro-enteritic epidemic in the Pediatric Dep. of the Rigshospital. It was demonstrated for the first time about 1 ½ years before in a child with gastro-enteritis admitted to Queen Louise's Children's Hospital.

All the strains belonging to this group have been identical fermentatively as well as serologically, being characterized in particular as far as their fermentative power is concerned by the late fermentation of xylose. Further, both groups are characterized by being hemolytic — a rare quality among the other colon strains isolated from infants.

In a number of cases the blood was examined for specific antibodies, but such could not be demonstrated — which perhaps was to be expected, as infants usually are poor antibody producers.

In animal experiments the strains belonging to the two groups mentioned were not more pathogenic than other colon strains.

In 48 cases of this apparently particularly malignant form of gastro-enteritis, bacteriological autopsy was performed under sterile precautions. About one half of the autopsies was performed by one of us (K.B.-S. or S.T.) with the following technique. After disinfection of the skin the body cavities were opened as sterilly as possible, and sterile instruments were employed for the removal of pieces of the organs, sample of the blood, etc., which were placed in sterile test tubes and at once sent to the Serum Institute, where cultures were made in broth and Kauffmann's tetrathionate medium, on blood plate and bromthymol blue-lactose agar. Aerobic incubation. For the rest, the same methods as are employed for the diagnosis of intestinal bacteria. Particular attention was paid to the possible occurrence of microbes that in this connection conceivably might be pathogenic. The results obtained are recorded in Table 1.

Table 1.

Bacteriological Autopsy Findings in Fatal Cases of Gastro-enteritis in Infants.

Large intestine	Gärtner Jena	Gärtner Jena	Gärtner Jena	Proteus	$\begin{array}{c} \textbf{Proteus} \\ + \textbf{colon} \end{array}$	Colon	Proteus	$\begin{array}{c} \textbf{Proteus} \\ + \textbf{colon} \end{array}$	Colon	Proteus + colon		Colon	
Small	Gärtner Jena	Proteus + colon	Proteus + colon	Proteus	Proteus + colon	Colon	Proteus + colon					Colon	
Lung		•				Colon-like rods			0	Proteus + colon	0		0
Mesenteric	Gärtner Jena	0	0	Proteus	Proteus + colon		0			Proteus + colon		Colon Pneu- mococ. Type 19	
Spleen	Gärtner Jena	0	0	Proteus	0	0	0	0	Colon	Colon		Colon	0
Liver	Gäriner Jena	0	0	Proteus	0	0	A few colon bact.	0	0	Colon	0	Colon	0
Heart's blood	Gärtner Jena	0	0	Proteus	Hem. strept. + colon	0	A few colon bact.	0	Hem. strept. Enterococei	Colon	Staph. albus	Colon	0
Autopsy No.	F. 16 223/43	F. 16 222/43	F. 16 221/43	F. 16 834/43	F. 16835/43	F. 17 607/43	F. 17 756/43	F. 17 881/43	F. 17 930/43	F. 17 931/43	F. 17 932/43	F. 17 933/43	F. 18 037/43

Proteus

	0	0	0	0	0		0	Colon	Colon	0	Co	Solon	_	_	0	Co	Colon	0	0
0								on	on		Colon	Colon-like rod	0	0		Colon	on	0	
0	0	0	0	0	0	Colon	Colon	Colon	0	0	0		Colon	0	0	Colon	Colon	0	Proteus
0	0	0	0	0	0	Colon	0	Colon	0	Colon	0	Colon-like rod	Colon	0	0	Colon	Colon	0	Proteus + colon
0	Staph, albus	0	0	0	0	0		Colon	Colon	0	Colon	Colon-like rod	Colon	$\begin{array}{c} \text{Proteus} \\ + \text{colon} \end{array}$	0	Colon		0	Proteus + colon
Colon	0			Enteroccoc.	0		Colon				Colon				0		Colon		Proteus + colon
Colon			Proteus + colon		Colon					Proteus + colon	Colon	Colon	Colon	Proteus + colon		Colon		Colon	Colon
Proteus + colon	Colon		Proteus + colon	Enteroc. + colon	Proteus + colon	Colon			Colon	Proteus + colon	Colon	Colon	Colon	Protens + colon		Colon		Protens + colon	Proteus + colon

0

0

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Table 1. (Conts.)

il Large ine intestine	colon Colon	olon Metacolon Ion + colon	albus 0	olon Metacolon Ion + colon	Colon	Colon	Droteus + colon	Colon	Proteus	on Colon + proteus	Colon	Colon	Colon + enterococ	Colon	roc. Proteus
Small	Proteus + colon	Metacolon + colon	Staph, albus	Metacolon + colon	Colon	Colon	Colon	Colon		Colon		Colon			Enteroe.
Inng					0			_		0				0	
Mesenteric	0		0	Metacolon	Colon	Colon	Colon	Colon	Proteus + colon			Colon		0	0
Spleen	0	Metacolon + colon	0	0	0	0	Colon	Colon	Proteus + colon	0	0	Colon-like rods	Colon	0	0
Liver	0	Colon	0	0	0	0	Colon	Colon	0	0	0	Colon-like rods	Colon	0	0
Heart's blood	0		0	0	0	0		0		0		Colon-like rods	0	0	0
Autopsy No.	F. 2 991/44	F. 4 060/441	F. 4144/44	F. 4 145/44	F. 4 372/44	F. 4771/44	F. 4867/44	F. 4 980/44	F. 6 306/44	F. 7 534/44	F. 8 023/44	F. 10 023/44	22 316/45	23 937/45	24 721/45

¹ On autopsy F. 4 060/44 a thoracic abscess yielded growth of metacolon bacteria in pure culture.

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From Table 1 it will be noticed that the first 3 cases yielded growth of Salmonella enteritidis Gärtner, Type Jena (these 3 cases belonged to a relatively small epidemic in Mrs. Hermansen's Clinic, where the diagnosis of enteritis Gärtner had been made beforehand), and that growth of pneumococci Type 19 was obtained from a mesenteric gland in autopsy F. 17933/43, whereas all the other cases only yielded growth of bacteria that ordinarily are not regarded as pathogenic intestinal bacteria. Two cases, F. 4060/44 and F. 4145/44 gave growth of metacolon bacilli or the so-called Morgan's bacillus No. 1 (Morgan 1909, Jordan 1935). It has always been a subject of discussion what role this bacillus plays in the occurrence of diarrhea in infants, but it has never been possible to demonstrate that it was definitely pathogenic. In case 4060/44 this bacillus was obtained in pure culture from a thoracic abscess and also from the spleen, and hence it seems justifiable in some degree to assign it a role in the fatal outcome of the case, although it is quite possible that it has appeared merely as a concomitant organism together with some unknown agent.

Otherwise the bacteria are distributed as might be expected in autopsy specimens where no particular measures are taken to prevent postmortal bacterial invasion. In several cases growth was obtained in cultures from the heart's blood, liver and spleen, but we should not venture to attach any particular importance to this, as it is not likely that all the autopsies have fulfilled the strictest requirements that ought to be made for a sterile autopsy. The colon bacteria here obtained were examined serologically, but neither of the above-mentioned groups could be demonstrated in any of the cases.

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Thus it has to be looked upon as rather questionable whether any etiological significance is to be attached to the colon bacteria with regard to the toxic gastro-enteritis. At any rate, the present examinations have not furnished any proof of this, and we think that after the results obtained the bacteriological findings do not allow of any descisive conclusion concerning a possible bacterial cause of the malignant gastro-enteritis apart from the few cases mentioned especially.

A priori, it cannot be taken for absolutely granted that the real cause of gastro-enteritis in infants is to be looked for in the intestinal canal. In the last couple of decades, increasing attention has been paid to the significance of parenteral infections (especially in the rhinopharynx and middle ear). On autopsy several authors have found almost pure cultures of streptococci from the lungs, liver and spleen, and they think that these bacteria are really the primary cause of the diarrhea, possibly through a secondary involvement of the intestinal canal (e.g., Chron, Shutter & Lahmann, 1940; Exner & Kotenetz, 1931).

As also these investigations appear not to offer any explanation of general validity, in more recent years there has been a steadily increasing tendency to attribute the malignant cholerine in infants to a virus infection. In particular, the cases of epidemic diarrhea of the newborn reported from America and England have given rise to very extensive investigations in order to demonstrate a virus as the possible cause — but also these efforts have failed to give any positive result.

In spite of this, most English and American authors are now inclined to assume a virus infection as the most probable, possibly combined with an increase in the virulence of microbes accidentally present (e.g., Crowley et al, 1941; Lyon & Folsom, 1941).

As the epidemics observed by us constitute a unity, clinically as well as epidemiologically, they might imply a fairly good chance of demonstrating a possible common etiological agent. As mentioned before, clinically, several points of resemblance to virus infections and their ways of spreading have been observed already. On this account, in the State Serum Institute, in the first months of 1944 a number of experiments were carried out in order to find whether a hitherto unknown ultravirus might be the cause of the disease described.

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As is well known, in experiments on isolation of virus the classical procedure is to give the animals injections of bacterially sterile suspensions of fluids or organs from the individual »suspected» of containing the virus.

A priori, the task here looked very difficult, as no definite evidence could be obtained, as to which organ or secretion might contain the virus possibly present. Nor had other experiments with near-related viruses offered any suggestion as to which species of animals might be preferable for this purpose.

For starting material we therefore employed any sort of secretion or excretion available, e.g., rhinopharyngeal secretion, spinal fluid, duodenal contents, and feces. Blood is difficult to obtain from such small children (<1 year) and has been employed only in one experiment. Of autopsy material, on the other hand, we have employed almost every organ (brain, spinal cord, liver, spleen, lung, lymph nodes, kidney, large intestine, small intestine, and intestinal contents taken from various sections of the gut).

For test animals we have used nearly all the laboratory animals commonly employed, that is, white mice, white rats, guinea-pigs, and rabbits; in addition a few hamsters, ferrets and one young monkey. The experiments comprise about 700 animals in all.

As the disease under investigation attacks selectively children under one year we employed only infantile or very young animals.

In order to avoid attenuation of the virus after its collection, we were careful to see that the material which was to be examined for virus should be brought to the Serum Institute as soon as possible and there employed at once for the experiments.

Clear and slightly opalescent fluids may be ultrafiltrated directly. Organs and similar materials have to be minced first and ground with quartz or fine sand in a mortar to a 10 % suspension in broth or saline. After centrifuging (6 000 revolutions per min. for 10 min.) the supernatant fluid is clarified by filtration through paper pulp or asbestos pulp.

As all the experiments turned out negative it will suffice to mention them briefly and quite summarily.

In about $3^{1}/_{2}$ months altogether 14 experiments were carried out, 9 with fresh material, 5 with autopsy material.

In other diseases the virus content of the organism is known

to be greatest early in the disease. In the present illness it is difficult at the onset to decide whether the lesion be a mild form of enteritis or the malignant form, and all the patients examined were therefore selected among the epidemiologically most certain and typical cases.

For inoculation — besides oral administration, which was employed in several experiments — we have tried subcutaneous, intravenous, intraperitoneal, intranasal and intracerebral injection.

In each experiment groups of the various animals were inoculated with the »virus suspension», always several animals of the same species — for instance, 5—6 mice, 2—3 guinea-pigs, and so on. To begin with, groups of untreated controls were included in every experiment. Towards the last, as all the experiments turned out negative, the controls were left out as unnecessary.

All the animals were inspected once or twice a day, at least for 4 weeks, often longer.

In several cases, moreover, blind passages (up to 5) were carried out, that is, material was transferred from symptom-free inoculated animals to fresh animals in order, if possible, to accustom the virus to the new host and obtain takes in a new passage. These blind passages were carried out at intervals of 4—10 days with employment of brain, liver, lung and spleen. Most of the blind passages were carried out on mice and rabbits (about 300 altogether), as these were the only animals that showed any symptoms at all.

In the mice the symptoms were debility and thin mucoid stools. For a while these symptoms seemed to promise a solution of the task, but then they proved to be due to a coincident epizootic in the mouse stock of the institute (infection with Bac. piliformis).

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Among the young rabbits a few had diarrhea which subsequently terminated fatally. But, as the controls behaved in the same way, this possibility vanished too.

On autopsy, macroscopic examination was made of the brain, lungs, liver, spleen, kidneys, lymph nodes and intestines; microscopic examination was made only in a few cases. In no instance did the examination reveal any abnormality that might be associated with the experiment.

In passing, it is to be mentioned that a few experiments were made on cultivation in eggs (injection into the allantoic cavity) with passage to mice. But these experiments also turned out negative.

In each experiment we had to make our choice as to which organs (or mixture of organs) and which animal species and injection methods were to be employed, as a systematic try-out of all possibilities was impracticable.

These experiments have not afforded any evidence to the effect that a virus has been the cause of the cases of illness here concerned. But this possibility still exists, and the experiments will be continued.

Summary.

In order to find out the cause of the malignant gastro-enteritis in infants, the stools from such children have been submitted to thorough bacteriological and serological examination.

In a good many cases, furthermore, autopsy was performed under sterile precautions.

As the bacteriological findings were not suggestive of any bacterial cause, attempts were made to isolate a possibly present virus. These attempts also proved negative.

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Purpura Fulminans and its Relation to Scarlatina.

By

HENRY FRÖDIN.

Scarlatina is a disease which has a marked tendency to carry manifold complications. Among those rarely observed are purpura diseases of varying degrees. A case of the very rare and most acute form, purpura fulminans, was recently observed at the Stockholm Hospital for infectious Diseases. As previously but few cases of this disease have been described, none of these being found in the Scandinavian literature, it seems justifiable to publish a detailed report of the case and in this connection a short survey of earlier cases of scarlatina with purpura from the Stockholm Hospital for infectious Diseases and also, discussing the patogenesis, a brief review of the literature in this field.

Case History: The case was that of a boy aged 5 years (b. Oct. 25, 1940), J. 135/46, transferred from the Sundbyberg Hospital for infectious Diseases to the Stockholm Hospital for infectious Diseases on Jan. 15th 1946, with acute onset of profuse extravasation with following serious anemia leading to death 48 hours later.

Hereditarly nothing remarkable, no cases of bleeder diseases in the family as far as known. The patient had not previously showed signs of hemophilia and had with the exception of banal disorders of the respiratory tract always been quite healthy.

The patient was taken ill around Nov. 12th 1945 with pyrexia and sore throat but no rash was observed. A coincident swelling of the left side of the throat increased gradually. Discharge from the right ear some days later. Medical advice was not sought until Nov. 11, on which

scarlatina desquamation was established and the patient sent to the Sundbyberg Hospital for infectious Diseases.

On admission Nov. 11 patient was pale, poorly nourished and affected with coryza. Slight circular desquamation of the digitis which subsequently increased, showing an appearance typical for scarlatina. There was further a rather firm slightly tender lymphadenitis the size of a plum at the left mandibular angle, a similiar bean-sized node at the right. No signs of breaking down. Internal organs normal. No disturbance of the reflexes. No signs of meningitis. No hemolytic streptococci were demonstrable in the throat. Examination by otologist Nov. 27: Left membrana tympani reddened, slight discharge from the tubar tract, right membran palish red, bulging. Bilateral paracentesis: slight returns. The discharge abates Nov. 30.

Sulfathiazole was given in the routine dose from Nov. 26 to Dec. 4. Patient afebril since admission. As the lymphadenitis on the throat after withdrawal of the preparation revealed a tendency to increase, a renewed course of sulfathiazole was given from Dec. 12 to Dec. 20, during which the lymphadenitis subsided markedly to the size of a pea. Patient now did well and only showed slight reddening and swelling of the throat in addition to an increased SR (Nov. 27: 68, Dec. 12: 60, Dec. 15: 62, Dec. 24: 45, and Jan. 1: 31 mm). Cor reveals a slight systolic murmur but eeg Dec. 12 and Jan. 8 showed neg. T 3, in other respects nothing remarkable. Urine normal. Mantoux 1 mg neg. Nov. 11 and Jan. 14.

Jan. 8 1946 for no appearent reason such as medication a subfebril temperature set in and numerous pinhead- to pea-sized erythematous lesions of the type erythema exsudativum multiforme appeared on the forearms and the legs below the knee. Coincidently a slight reddening of the throat developed with a small plug in the left tonsil. Nothing else pathological from the internal organs. The symptoms disappeared after two days.

Jan. 14 a bluish discolored slightly tender infiltration appr. the size of a child's hand was observed on the right lower extremity. No other abnormality was noted. During the night, new ecchymosis on both lower extremities, small petechiae on the trunk and hematuria. Praeputium somewhat swollen.

Leucocyt count, which on Dec. 12 was 7 500 and Dec. 16 13 900 had by Jan. 14 increased to 20 600. Differential Jan. 14: stabforms 9 %, segments 72 %, eosinophils 1 %, basophils 1 %, lymphocyts 10 %, monocytes 7 %. Hb Jan. 14 70 %.

Patient transferred to the Stockholm Hospital for infectious Diseases on the afternoon of Jan. 15 1946.

On admission here pale, poorly nourished, ill-looking. Temp. 38°3, pulse rate 120. The skin revealed no desquamation or exanthema. Over the left hip and on both lower extremities ecchymoses in the form of purple tender infiltrations, varying in size from the palm of a child to that of an adult. Small petechial hemorrhage on lower portion of the back. Throat: tender conglomeration the size of a plum at the left

mandibular angle, nothing else palpable. Lungs and heart: no remark. Blood pressure: 130/70 mm. Abdomen: Nothing patological palpable. Pupillar-, patellar- and achilles-reflexes normal. Moderat swelling of preputium, insignificent discharge. Weight 17 kg. A septic condition was suspected and in consideration of the contingency of hypersensitiveness to sulphapreparations penicillin in dosis of 15 000 Oxford units every three hours was prescribed.

The day following admission, Jan. 16, the general condition was rather improved. Pat. was quite brisk and had a good appetite, but the echymoses had increased somewhat in size, the infiltration over the left hip and both lower extremities being swollen and tender. Urine still macroscopical bloody. Slight bleeding from lips and gums but no hematemesis or melena. Temp. 37°9-38°8, pulse rate 100-120/min. Blood count: Hb 60 %, red cells 3.7 million, color index = 1.0, white cells 10 500, SR 28/65 mm. Differential: stabs 1 %, segments 79 %, mono. 4 %, lympho. 16 %. Platelets 222 000. Blood culture: no growth on aerob or anaerob culture. Bleeding time 27 1/2 min., coagulation time 19 1/2 min. (normal time 7 min.). Göthlins test: 50 mm Hg during 15 min. gave no new hemorrhages within the area outlined (the previous day a number of petechial hemorrhages would have appeared after the routine blood pressure measurement), pin prick tests showed hemorrhages the size of a pin's head around the punctures, percussion test on the anterior aspect of tibia neg. Further examinations: Urine: Esbach 0.6 pro mille, abundant red cells in sediment. Rest-N 28 mg%. Ecg normal. Hemolytic streptococci in throat +.

The penicillin dose was raised to 30 000 Oxford units every third hour and blood transfusion of 180 cc citrated blood from donor of the same groups (AB) was given, without immidiate complications.

The following day, Jan. 17, the general condition was much poorer. Very pale and tired, but mentally clear and taking fluids and food surprisingly well. Drop of temp. to 36%. Pulse rate 144. Blood pressure dropped to 60/10 mm Hg. No further bleeding from the oral cavity but some oozing from the nose. Urine still bloody. Ecchymoses considerably increased. On the outer aspects of the thighs, on the right side covering the trochanter region and on the left stretching from this downwards over 2/3 of the thigh and also involving a portion of the frontal and dorsal aspects thereof. Large infiltrations on both lower extremities, dorsally extending from dorsum well halfway to the popliteal space, a rather large infiltration on the left side where transfusion was given supramalleolarly. Smaller ecchymose, at the most 2 1/2 cm wide on the upper extremities. Numerous not more than pin-head sized petechiae here and there on extremities and back. Throat and gums not abnormal. Lymphatics: swollen glands at left angulus unchanged. Lungs: nothing abnormal. Heart: tachycardia, no other pathological signs. Abdomen: liver palpable the bredth of a finger below the costal margin, nothing remarkable, spleen not palp. Blood values had in spite of transfusion dropped to Hb 35 %, red cells 1.4 million, color index 1.46. White cells 20 000 (polymorphonuclears 70 %, mononuclears 30 %). Platelets 210 000. Blood sugar 358 mg%, some hours later 230 mg%. Prothrombin test: no coagulation. Total albumin in serum 5.9 %: albumin 3.2 %, globulin thus 2.7 %, quotient 1.2. Fibrinogen content unfortunately not determined. Serum ascorbic acid below 0.1 mg% (by mistake the sample was not determined until after the lapse of four days, the value thus being uncertain). A certain suspision that the deterioration of the patients condition was due to the transfusion was not supported by the declaration from the State Forensic Chemical Laboratory, according to which the blood grouping combination of the patient was A, BMNRh(+), there was no irregular agglutinin in serum, no substantiation for Rh-immunisation, nor had the patient previously been given any transfusion.

The patient was treated with copious stimulants in the form of sympatol and cortiron, K-vimin and C-vimin in large doses were further administrated by injection, and finally at noon a renewed transfusion of 250 cc of AB-citrated blood was given. Following transfusion the condition was somewhat improved, the patient took fluids but had occasional small vomiting attacks. Blood pressure rose to 90/40 mm, the blood values to Hb 48 %, red cells 3.47 million, color index 0.7, temp. 38°5, pulse rate 153 (3 p. m.). No new hemorrhages. At 5 p. m. a marked deterioration of the general condition set in with convulsions and temporary unconsciousness. At 6.45 p. m. a renewed transfusion was to have been done, but before it was carried out the patient collapsed and died.

Clinical diagnoses: Purpura fulminans (post scarlatina) + lymphadenitis ac. colli sin. + septichemia(?).

Necropsy 24 hours after death (doc. RINGERTZ).

Developement and nutrition normal. Skin markedly pale. On both thighs and lower portions of the legs bluish-red areas of the skin the size of a palm associated with diffuse swelling. Section reveals dense subcutaneous extravasation and deep in the musculatur scattered small extravasations. Body cavities and serosa not remarkable. Retroperitoneally in the left renal tract an immense extravasation. Heart and lungs not remarkable. Mediastinal lymph nodes slightly swollen. Throat: slight reddening of mucosa, tonsils rather larger than filberts, red and plugged. Upper cervical lymphatics nearly the size of a pigeons egg, greyish red, soft, section surface smoth. Lower lymphatics the size of a navy been similiar appearance. Liver normal in size, pale, cyanotic, mottled markings, turgescent parenchyma. Biliary duets and pancreas not remarkable. Spleen: normal size, quite firm, pulpagreyish white, negligible follicle

markings, negligible scrapings. Adrenal glands: left surrounded by recent hemorrhage, in other respects not remarkable, right normal. Kidneys: normal size, parenchymatous degeneration, on the surface scattered minute red points. Urinary canal normal. Digestive tract normal. Mesenterial glands: at the angle of caecum a hazel-sized conglomeration of greyish-red soft glands, similiar pea-sized glands in the coeliac region. Groin lymphatics bean-sized, slightly reddened. Axillary lymph nodes pea-sized. Bone-marrow of femur diaphysis greyish-red.

Microscopical examination: Lymph nodes: universal non-specific marked lymphadenitis. Cervical lymphatics revealed in addition chronic inflammatory changes with capsular swelling. Spleen: Infectious picture. Liver: Slight parenchymous degeneration. Bone-marrow: moderately active marrow with normal cell picture, megacaryocytes somewhat degerated. Bacterial culture (sterilly obtained organ material): Liver, spleen, kidney and lymphatics gave no growth of aerob or anaerob bacteria.

Pathological-anatomical diagnosis: Tonsillopharyngitis acuta + Lymphadenitis universalis + Diathesis hemorrhagica (septica).

Summary of case history: A boy, 5 years of age, previously healthy and without heredity for hemophilia is taken acutely ill with sore throat and pyrexia. Medical advice is not sought until after two weeks when swelling on the left side of the neck and discharge pus from the right ear set in. The patient at this time showed a distinct scarlatina desquamation and was sent to the Sundbyberg Hospital for infectious Diseases. On admission afebril, pale, poorly nourished, cervical adenitis, slight bilateral otitis which after paracentes heals rapidly. Sulphathiazole medication with full doses for two periods of 10 and 8 days, respectively, upon which the symptoms recede. Uncomplicated further course. SR drops gradually from 68 to 31 mm/hour. On the 57th day after onset a typical erythema exsudativum multiforme appears with subfebril temperature, the symptoms disappearing after two days. On the 63d day (after 9 weeks) ecchymoses appear on the right leg below the knee, later spreading to both legs in the form of large swollen tender purple infiltrations. Pat. is the following day transferred to the Stockholm Hospital for infectious Diseases. On admission here pale, poorly nourished, ill-looking. Large subcutaneous extravasations on the lower extremities, in addition small petecchiae on the trunk and all extremities. Urine bloody. Small hemorrhages from nose and gums. Tender adenitis at the mandibular angles. Slight reddening of the throat, hypertrophic tonsils. Moderate swelling and discharge from praeputium. Temp. 38°3. The next day (the 65th) unaltered condition. The pat. is given penicillin in a large dose as the morbid picture is considered suspect for sepsis and sulpha-preparations are considered to be contraindicated due to the possibility of hypersensitiveness. Blood transfusion is also given. In spite of these measures the general condition deteriorates considerably during the night, the temperature becomes subnormal, the pulse rate high, falling blood-pressure, considerable increase of extravasation, blood values drop from 60 %, 3.1 million to 35 %, 1.4 mill. Maximally prolonged bleeding-, coagulation- and prothrombintime. Platelet count 210 000. Blood culture neg. Blood ascorbic acid decreased, blood albumin normal (fibrinogen unfortunately not examined). Transfusion complication is discussed but not considered probable according to declaration from the State Forensic Chemical Laboratory. A renewed transfusion is given, as well as large doses of sympatol, cortin, C-vimin, K-vimin, but the case goes ad mortem the same evening, on the 66th day after the onset of scarlatina and three days after observation of the first extravasation. Necropsy (doc. RINGERTZ): reveals acute tonsillopharyngitis, an universal septic lymphadenitis, large subcutaneous extravasations of the lower extremities extending far into the musculature, a large hemorrhage proximal to the right kidney, both adrenal glands, however, being normal. Parenchymous degeneration and small hemorrhages of the kidneys, turgescent mottled liver parenchyma, infectious picture of the spleen. Bacterial culture from various organs negative, but the pathological anatomical picture especially of the lymph nodes resembled sepsis.

Diagnosis: Purpura fulminans (post scarlatina) + lymphadenitis acuta universalis + septichemia(?)

A survey of the purpura cases at the Stockholm Hospital for infectious Diseases during the years 1921—1945 has been done in an endeavour to illuminate a possible relationship between scarlatina and purpura.

Altogether taken, 39 cases of different purpura diseases have been traced. Of these but 6 may be connected with scarlatina. During these 25 years approximately 23 000 cases of scarlatina were treated at the Hospital. All of the purpura cases recovered, none of the cases were of the purpura fulminans type. 6 of the cases were associated with thromboeytopenia, but none of these cases were associated with scarlatina. In the scarlatina group but one case had so low a platelet count as to border on pathological values. Of the athromboeytopenic cases in the group with absence of scarlatina, one case was associated with syphilis, two cases with intoxication mercurialis, one case with lymphadenitis submaxillaris, two cases with febris rheumatica, and one case with

paratyphoid. — A brief report will be presented of the six instances of purpura, in which, similiar to the case just described, a more or less definite association with scarlatina is established.

Case I: J. 154-28, male, 7 years of age. Diagnosis: Purpura + glomerulonephritis ac. Previously healthy. After throat infection of two weeks standing the pat. was admitted to a Childrens Hospital with the diagnosis of purpura rheumatica. After 12 days a papular exanthema appeared in the flanks in addition to red strawberry tongue, after which the pat. was transferred to the Stockholm Hospital for infectious Diseases. Examination on admission: Hb 80 %, red count 6.3 million, white count 9 400, bleeding time 4 min. Typical red strawberry tongue, reddening of the throat, no exanthema. Hemolytic streptococci in throat pos. Over the gluteal region and downwards small papular hemorrhagic spots. In the urine numerous red cells and granular casts. Platelets 342 000. During the second week at the Hospital typical desquamation of the fingers in large flakes. The purpura ecchymoses disappeared after a few weeks, the further course was uneventful. From the data it will be seen that the morbid picture markedly resembles that of scarlatina, although this diagnosis was not made.

Case II: J. 781—29, female, 5 years of age. Diagnosis: Scarlatina + purpura? + parotitis epidemica + otitis suppurativa dxt. + lymphadenitis colli. Previously healthy. Typical onset of scarlatina with sore throat, pyrexia, exanthema. Temp. appr. 39° during one week, on the 6th day acute cervical lymphoma, on the 8th day symmetrical purpura ecchymoses on the dorsum, which faded and vanished after 6 days. Hb 76%, red count 4.0 mill., white 16 800. Platelets 320 000. Further course uneventful, apart from parotitis and otitis which healed smoothly.

Case III: J. 320-38, male, 2 years of age. Diagnosis: Scarlatina + purpura hemorrhagica. Previously healthy. Typical onset of scarlatina with sore throat, pyrexia, exanthema. On the 12th day symmetrical purpura ecchymoses over the shoulders and dorsal aspects of the extremities, as well as on scalp and face. Before the onset of the purpura the pat. had received prontosil, 1/4 tablet thrice daily for 6 days, the medication having been administered as routine terapy for scarlatina. No complications such as lymphadenitis, fever, etc. The prontosil, which was considered to be the cause of the purpura, was withdrawn. Hb 75 %, red count 5.38 million, white count 11 100. Platelets 513 000. On the 10th day after the disappearance of the ecchymoses a new crop of purpuric spots appeared on face, neck, chest and legs below the knees. Hb 68 %, red count 4.95 million, platelets 321 000. The further course was smooth. The diagnosis is probably erroneous, purpura simplex being more correct. No hemorrhage from mucous membranes are described.

Case IV: J. 684—38, male, 4 years of age. Diagnosis: Scarlatina + purpura + lymphadenitis colli + otitis + herpes zoster. Previously healthy. Three days prior to admission fever, right-sided otitis. On admission slight reddening of the throat, pale exanthema on the back and sides of trunk. Large cervical adenitis, the ears healed. The scarlatina diagnosis was considered certain. On the 17th day after the first onset (14th day after appearance of exanthema) petechiae appeared on neck and shoulders, simultaneously with typical desquamation. Hb 73%, red count 4.27 million, white count 6 500. Platelets 180 000. The petechiae disappeared after 10 days. Discharged healthy.

Case V: J. 1105-44, male, 5 years of age. Diagnosis: Scarlatina + vulnus infectum penis + lymphadenitis colli acuta + morbilli + purpura hemorrhagica (sulfa?). Previously healthy. Three days prior to admission lesion on penis which was sutured, infection of the lesion following; on admission scarlatina-like exanthema, reddening of the throat, red strawberry tongue, positive blanching reaction. On the 42nd day after the onset of the exanthema and following three days of sulphathiazole medication in doses of 0.5 g thrice daily (administered as therapy for the lymphadenitis) morbilli supervened and on the 45th day, symptoms of angina tonsillaris which occasioned a renewed sulphathiazole course for three days with a daily dosage of 1+1+0.5 g every 4th hour. The medication was discontinued on the 53d day as purpura hemorrhagica supervened in the form of oral and nasal hemorrhages, blood in feces and urine, and wide-spread petechiae on the extremities. The blood values fell to Hb 41 %, red count 1.95 million, white count 14 000. Platelets 52 000. Transfusion was given after three days of hemorrhages. Following this, a good recovery was made, and the blood values rose to Hb 60 %, red count 3.46 million.

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Case VI: J. 2429—45, male, 2 years of age. Diagnosis: Scarlatina + urticaria manu bilat. + purpura simplex + rhinitis acuta. Previously healthy. Acute onset with pyrexia, vomitus, exanthema, blanching reaction positive. Hemolytic streptococci in throat ++. Smooth course until the 17th day, when oedema of the Quincke type appeared on the dorsal aspects of both hands. By the 21st day the oedema had disappeared but purpuric spots on the extremities appeared instead. Platelets 98 000, 5 days later 202 000. Hb 68 %, red count 4.25 million, white count 10 800. Bleeding time $4^{-1}/_{2}$ min. After 10 days the spots disappeared and the pat. was discharged cured.

In connection with the case histories reported, some data on purpura fulminans, its possible relationship to scarlatina, and purpura conditions in general in association with scarlatina will be presented.

Purpura fulminans is a malignant form of the purpura disease, progressing with large extravasations and subsequent acute anemia, usually fatal within two days. The disease is very rare, not more than approximately 100 cases thereof having been described in the literature. One fourth of these cases have been associated with scarlatina. A survey from 1910 (Mac Cririck (5),(7)), the most recent which it has been possible to trace, comprices 64 cases, among which 17 were associated with scarlatina. Reports in the recent literature seem to be rare. Of late, however, the conception purpura fulminans is more frequently used, but nearly exclusively in regards to the Waterhouse-Friedrichsens syndrome: thus meningococcsepsis with adrenal hemorrhages, a morbid picture where ecchymoses are present, it is true, but generally not confluent to immense infiltrations, comprising the cardinal symptom.

Descriptions of the true purpura fulminans cases are fairly uniform. Hereditarly there is usually no hemphilia, nor is it found earlier in the anamnesis. In the majority of the cases the disease affects children, especially of tender age and there is no sex difference. The patient has as a rule one to four weeks previously passed through a generally not especially severe disease, such as scarlatina, morbilli, varicellae, difteria, angina tonsillaris, pneumonia, etc.; but in several cases, especially in infants, the onset is sudden as a bolt from the blue. The injection of serum has also been reported as causative. HENOCH, who named the disease, described two own cases and reported two other cases from the literature already 1887 (8), one of his own cases being that of a boy 5 years old, with the onset one week after a pneumonia crisis, and leading to death within 24 hours; his other case was that of a girl, 21/2 years of age, with onset two weeks after scarlatina and with the same swift letal course.

The onset of the symptoms is usually acute with small purple subcutaneous ecchymoses, which spread within a few hours to the size of palm of a hand or larger. Between these large ecchymoses numerous smaller petechiae usually appear. The most frequent localisations are the extremities, particularly the lower ones, where especially the dorsal aspects of the legs below the knee and

¹⁵⁻⁴⁷³²² Acta Padiatrica, Vol. XXXIV

the outer aspects of the tighs up to the trochanter region are involved. Occasionally ecchymoses are observed in the lumbar region, and sometimes also in the face, where especially cheeks and nose are involved. The ecchymoses are often symmetrical. More or less pronounced hemorrhages from the mucosa are observed in a number of cases, usually from nose and mouth, occasionally in the bowels or from genital organs. Hematuria is quite common, usually with renal origin, occasionally from the mucosa of the bladder. The external hemorrhages are not usually fatal per se. Pyrexia and leucocytosis is usually present, in varying degrees, but may be absent. Eosinophilia is frequently present. The platelet count is usually within the boundaries of the normal but may be decreased. Bleeding time and coagulation time are frequently maximally prolonged. Afibrogenemia and hypocalcemia have been described but are not characteristic. Capillary resistance test (RUMPEL-LEED) may be positive or negative.

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In the further course of the disease, the ecchymoses spread and may in serious cases involve an entire extremity, while an increasingly serious anemia developes, evidently because of the loss of blood to subcutis. The general condition deteriorates rapidly and death usually follows after one or two days, in extreme cases from five hours to four days. Some few cases which have recovered have also been described (cf. KNAUER (10)). Sub finem vitae mental symptoms such as convulsions and unconsciousness are occasionally observed but remarkably often the patient is mentally clear to the end. It is characteristic of the hemorrhages that previously intact skin is involved, thrombostasis etc. usually not occuring. Occasionally the skin may show secondary changes with the development of bullae containing a serous bloody fluid, in some instances progressing to necrosis and gangrene. Besides these large subcutaneous extravasations extending into the deeper tissues and a markedly pronounced anemia in all of the organs, little else is generally found at the necropsy. Hemorrhages of the internal organs may occur. Toxic lesions of parenchymous organs, brain, lymphatics etc., have been described. Adrenal gland lesions are infrequent. Signs of sepsis are not usual. Bacterial cultures may be positive, e.g. hemolytic streptococci

(Hunt (9)). Terapy is usually hopeless. First and foremost blood injections and repeated large transfusions have been given. Vitamin C, Vitamin K, calcium, extract of liver, coagulen, gelatin, antistreptococcous serum etc. have all been administered without palpable effect.

The etiologi of these peculiar morbid conditions is in no wise satisfactorily explained. It is probably not homogenous. Although the clinical course of the various cases is fairly similiar, the blood- and bleeding-tests show wide divergences in the different cases. There signs of as well disturbances of the mecanism of coagulation as of augmented vascular permeability. In the former case we may have to deal with a deficiency of fibrinogen (cf. KNAUER (10)), probably caused by a hepatic lesion, or a thrombocytopenia may be the cause of the disturbance of coagulation. This thrombocytopenia is frequently temporary and has been interpreted either as secondary to a toxic lesion of the bone-marrow, or else as being due to a great number of the platelets having been withdrawn from the circulation in order to repair defects of the capillary endothelium (Wood-Smith (18)). Disturbances of the vitamin-K-prothrombin mechanism, brought about by toxic hepatic lesions may also be considered as etiological for disturbances of coagulation, the prothrombin time sometimes being markedly prolonged. In sepsis a »thrombolytic purpura» has been described i. e., a surplus of thrombolytic ferment is produced by the leucocytes, coagulation developing normally, but the coagulum formed, however, soon being dissolved again (Reimer (15)). This might accordingly be considered etiologic in some of the septic cases. The symmetrical tendency of the ecchymoses have been considered a substantiation for a central genesis, in the form of toxic lesions of the brain substance (SÜNDER (17)).

The most comprehensive theory for the genesis of the hemorrhages is that they are caused by toxic and above all allergically conditioned changes of the permeability of the blood vessels. We should accordingly have to deal with a serious form of anaphylactoid purpura (Schönlein-Henoch), and thus a difference of degree rather than of character, between common anaphylactoid purpura and purpura fulminans. The fact that both

forms relatively seldom show external hemorrhages, contrary to e.g. thrombocytopenic purpura, indicates a correlation. Purpura fulminans has been observed following the injection of serum in cases where the patient previously has been given serum and thus has been sensitized (BRÜHL (2)). In many instances, such as in the present case, allergic erythema have been observed in association with purpura fulminans. Eosinophilia occurs in numerous cases. The term »hemorrhagic allergy» has been created (Sanarelli, cf. GLANZMAN (7)). This worker injected bacterial filtrate, first subcutaneously and 24 hours later intravenously obtaining necrotising and hemorrhagic reactions locally at the site of the initial inoculation. It is hardly likely that bacterial toxins are the primary cause of purpura, as this latter generally occurs a couple of weeks after the onset of the infection, and but rarely in the initial period when the toxin content is greatest (HUNT(9)). It is more reasonable to assume that an allergy for the bacterial toxins occurs in connection with the first onset of the infectious disease and that the anaphylactoid purpura reaction occurs at a potential recidivation of the disease with an augmentation of the toxins (GLANZMAN (7)). This is appearently the most comprehensive theory regarding the etiologi of purpura fulminans.

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As was mentioned above, approximately one-fourth of the purpura fulminans cases are associated with scarlatina. Other forms of purpura also occur in scarlatina, and here also there is probably a difference of degree rather than of type, between the mild cases of purpura merely showing small petechiae without deterioration of the general condition, and the serious cases, often associated with hemorrhages from the mucosa, and finally the lethal cases of purpura fulminans. Distinction is made between two periods for the onset of purpura in association with scarlatina: firstly, the initial stage, in the milder cases in the form of a hemorrhagic exanthema which may progress directly to severe manifestations of extravasations, even purpura fulminans, and secondly, more frequently, from the second to the fourth week; occasional cases, however, are described as developing as late as eight weeks after the onset of the scarlatina (MAC CONNEL-WEA-VER (5)). The cases in the secondary stage are often heralded by a

rhinitis, tonsillitis, lymphadenitis, subfebrile temperature, albuminuria etc. etc., thus a flare of the streptococcus infection with an increased excretion of toxins. The occurrence of purpura has in other respects no relation to the degree of the scarlatina, the most serious instances of purpura frequently occurring in association with mild atoxic scarlatina infections. Of interest is the assertion that the initial hemorrhagic nephritis is occasioned by a capillary lesion of the kidneys of the same appearance as the capillary lesion of the skin in purpura, the nephritis in question being termed renal purpura (Hunt (9)). Investigations have revealed that Rumpel-Leeds test of capillary resistance to a great extent is positive during scarlatina, this disease accordingly predisposing towards a capillary fragility, which in rare and serious cases is manifest by purpura (HUNT(9)). As mentioned above, the capillary fragility is probably toxically-allergically determined. Lesions due to bacterial emboli in the skin have also been suggested as a causative factor, this, however, being less probable, as the blood cultures usually are negative. If scarlatina thus should predispose towards purpura there is on the other hand no evidence of purpura prior to scarlatina infection having any tendency to recur in association with scarlatina. In regards to the frequency of purpura diseases in association with scarlatina a survey of the literature (Hunt (9)) reveals approximately 62 cases of purpura in association with scarlatina, less than fifty per cent thereof being of the fulminant type. The same author has in a series of about 5 000 scarlatina cases not found more than two instances of purpura, one of them being fatal.

Finally, a short *epicrisis* will be presented, principally in regards to the present case. The morbid picture, with acute onset of enormous extravasations in a child convalescent from an infectious disease, the rapid course with increasing anemia and resistance to therapy leading to death within 3 days, is fully typical for purpura fulminans. As regards the etiology, this may probably be traced to the scarlatina assumed. It is true that no exanthema were observed but on the other hand a throat infection and later a typical desquamation within an appropriate period were ob-

served, in addition to complications typical for scarlatina, such as lymphadenitis and otitis, and if one wishes, also purpura. The onset of the purpura is remarkably late, in the 10th week as against the 8th week, previously reported as the latest extreme. On the other hand the persistent high sedimentation rate is an indication that the scarlatina at this late date had not yet been healed. It is not clear whether the origin of the purpura in this case is a sepsis occasioned by hemolytic streptococci or an anaphylactoid reaction following sensitization to streptococcus toxin. The necropsy findings indicate sepsis but growth from blood and internal organs was on the other hand negative. The erythema exsudativum multiforme appearing one week before the onset of purpura in association with low-grade fever and throat infection (flare of streptococcus toxin?!) speaks in favour of an allergic origin. The absence of hemophilia in family history and anamnesis and a normal platelet count argue against purpura with any other pathogenesis than anaphylactoid or possibly septic. The low blood ascorbic acid (below 0.1 %) is probably secondary and could not in any case explain the fulminant course of the disease.

In regards to the 6 milder cases of purpura described above, the frequency of purpura, 7 out of 23 000 cases of scarlatina shows how rarely this complication is found. These figures are in fairly good accordance with those of Hunt's (9) investigation, viz., 2 out of 5 000, where one of the purpura cases was of the fulminant type, while in the present series but one of the 7 purpura cases was fatal. The age of the previous purpura cases at the Stockholm Hospital for infectious Diseases has ranged between 2 and 7 years, 5 boys and 1 girl. The first case is uncertain, the purpura symptoms occurring about one week before the scarlatina exanthema. In four of the remaining cases the onset of purpura occurred from 7 to 21 days after the debut of the scarlatina. In the fifth case the onset was as late as the 53rd day after the scarlatina exanthema but in this case morbilli and angina tonsillaris had supervened some time before the onset of the purpura, and these disease may conceivably also be etiologic. In this case, as in Case III a sulfa-medication preceded the purpura (sulfathiazole

and prontosil, respectively) as a possible further etiology. As to complications, hemorrhagic nephritis was found in Case I, at about the same time as the purpura. Cervical adenitis preceded the purpura in Cases II and IV, angina tonsillaris + morbilli in Case V. One instance, Case VI, points directly towards an allergic etiology, Quinke's oedema preceding the purpura. The ecchymoses were in three of the cases, II, III, VI, markedly symmetrical. They were localized in such a manner that practically all portions of the body were represented: the lower extremities in two instances, the upper in one instance, the entire body in two instances, neck and shoulders in one, and face and scalp in one instance. The fifth case was rather more serious than the rest, with hemorrhages from the mucous membranes and pronounced anemia. In two instances, Cases V and VI, the platelet count was decreased touching on pathological values (52 000 and 98 000, respectively). Bleeding tests were not usually done, in Case VI the bleeding time was normal. In Case V the blood values fell to Hb 41 %, red count 1.95 million, for the rest the blood values were fairly normal. The leucocyte count was normal or moderately increased, most markedly in Case II: 16 800.

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Finally, it may on the basis of the foregoing analysis be considered that purpura fulminans is a very rare disease, but nevertheless of great practical and theoretical interest. Of practical interest, as the mortality nearly amounts to one hundred per cent, an efficacious treatment accordingly being of the greatest importance in saving many otherwise healthy children. Theoretically, the disease is of interest by its relationship to other purpura diseases (especially Schönlein-Henoch), as well as to the anaphylactoid reaction complex, thus particularly in regards to bacteria and their toxins, mainly scarlatina.

Summary. The object of the present study is a case of purpura fulminans in a boy of 5, treated at the Stockholm Hospital for infectious Diseases. The patient, previously healthy, was taken ill with a fairly mild, although drawn-out scarlatina infection, which judging from the high sedimentation rate had not healed when after the lapse of 9 weeks erythema exsudativum multi-

forme supervened and after another week large subcutaneous hemorrhages suddenly appeared, with increasing anemia and deterioration of the general condition leading to death in 3 days, notwithstanding vigorous therapy with inter alia large transfusions. Bleeding, coagulation and prothrombin times were maximally prolonged. The platelet count was not decreased. No bacteria were demonstrable in blood or internal organs but necropsy findings indicated sepsis. In connection with this case a survey was done of the purpura material of the Stockholm Hospital for infectious Diseases from the last 25 years, revealing that no previous case of purpura fulminans had occurred. Six of the purpura cases, all of them mild, were more or less associated with scarlatina and are described in detail. Furthermore, a brief description based on studies in the literature of purpura fulminans is presented, including its relationship to scarlatina, and purpura conditions in general in association with scarlatina. Purpura fulminans stands out as a rare but entirely typical disease, dominated by immense extravasations, with usually a rapid fatal course, generally in association with scarlatina or some other infectious disease. Therapy has in the majority of the cases been hopeless. The etiology is probably toxic-allergic, with bacteria or bacterial toxins as causative agents, and there is rather a distinction of degree than of form, from the milder purpura Schönlein-Henoch. A septic pathogenesis may also in a number of instances be considered. Finally, a brief epicrisis of the cases described is presented.

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Examinations on the Duration of the Period of Lactation and its Dependence on the Age of the Mother and other Factors.

By

GILLIS HERLITZ.

The question of the ability of mothers to suckle their children for a sufficiently long time is of central significance in pediatrics and has therefore been the subject of much discussion at all times. The social side of the problem has lately come more and more into the foreground owing to the increased number of women now in employment away from home. Lactation hindrances of a medical kind, as illnesses or deformities in the mother or child are rather unusual and therefore play a relatively small rôle when considering the question of lactation at large. The occurrence of real agalaktia is now denied by most pediatricians and gynæcologists (JANISCH) whereas on the other hand a socalled primary hypogalaktia is not regarded as all too unusual (Weiss and Hölzel, ENGEL, V. PFAUNDLER, BENDIX). Along with local anatomical (ENGEL) and inner secretional factors, also undernourishment (WAGNER, GELLER) and lack of E vitamin (THIEME) is mentioned as being of decisive significance in this matter. It is however, of importance to learn in what measure lactation ability normally varies with certain factors which prevail in all mothers but in a different degree in different cases. Concerning the age of mothers FRIEDLÄNDER has thus already pointed out that older mothers more often appear able to suckle their children than the young ones. Touching the duration of the period of lactation similar observations have been made by Bendix and lately in our

country, in a different connection, by Broman, Dahlberg and Lichtenstein.

It is naturally of great interest to a pediatrician to get more light on this question. If the older mothers are able to suckle longer than the younger ones it may of course depend on physical differences between them of inner secretional or of other nature connected with the very age factor as such and not with any other circumstances. However, it may also mean that the older mothers are more ambitious than the younger ones or that their children, on an average, have higher birth numbers than those of the younger ones, with all that this signifies for milk secretion and lactation technique. Possibly, differences in the weight at birth between the children of the older and younger mothers may play a rôle. An investigation of these conditions still seems necessary. There ought to be possibilities to examine the significance of at least part of the factors named if one has access to a sufficiently large and well-observed material where the feeding of the children has taken place under good as well as uniform control. I believe to have had such material at the Stockholm Municipal Child Welfare Centres and it is on this material that I have made a number of calculations with a view to obtaining some light on the above named conditions.

Material.

The material comprises 4084 infants, 2085 boys and 1999 girls representing the total number of children registered for the year 1939 in the Stockholm Child Welfare Centres and the feeding of which is known until their complete weaning has taken place. For each child has been registered, firstly the number of months it was given the breast only and secondly the number of months it was given allaitement mixte. The first period has been designated b, the second m; b has been regarded as concluded for each child as soon as cow's milk has begun to be mixed with the food, and m as soon as the mother has stopped giving the breast altogether. Artificial food other than cow's milk has not been taken as a substitute for mother's milk. No consideration has been taken to the inclusion of fruit juices or similar things usually given

in small quantities as extra vitamins, to accustom infants to new tastes at an early age and which as calories mostly lack significance. The entries in the journals have been sufficiently accurate to allow b and m to be rounded off to even fortnights; the registration has been made the whole time according to a uniform principle. Information as to the father's resp. mother's calling, mother's age, the birth number of the child and so on has also been obtained from the journals; if completions were required they were obtained from the Registrar General Stockholm.

In the year 1939 about 75 % of the children born living in Stockholm were registered at the Child Welfare Centres. Age at admission of the material collected here was on an average 1—2 months. 447 mothers of the material were unmarried. The distribution as to social Status was as follows: lowest class 75.9 %, lower and upper middle class 22.1 %, highest class 2.0 %.

At the Child Welfare Centres there has been a persistent endeavour to encourage the mothers to continue suckling without the inclusion of artificial food (other than fruit juices etc., see above) until the child has reached the age of at least 5—6 months. An age of 8—9 months has as a rule been regarded as the most suitable time for the definite cessation of suckling. Control of the feeding has been held during the subsequent visits of the mothers to the centres but also to a great extent in the homes during visits paid by the clinic nurses.

The mortality figure for Stockholm in 1939 for the first year of life of 1000 children born living was 32.1. Of these 85 % died in the two first months after birth. The number of children in the here observed material that died before reaching one year of age was 15, i. e. 0.37 %. The statements here given for all the children were obtained from the Registrar General for the reason that the fate of all the children have not been followed at the Centres up to the age of one year. In the case of 22 of the children, the authorites have been unable to give any information in consequence of their having left the town etc. If one reckons that the children were placed under observation at the age of two months, the mortality figure of 0.37 % is lower than might be expected when considering the above figure for the general in-

fant mortality after this age. The material must therefore be considered choice also regarding those factors which postulate infant mortality after the age of two months. This circumstance can however not affect the comparisons put up below between different fractions of the same.

For calculating the statistic characteristics (standard deviation, standard error and correlation coefficients) the customary formulas have been employed. When a difference has amounted to 2.5—3 times its standard error, it has been considered statistically probable (Dahlberg). Within the majority of the larger groups of material, the form of distribution has been examined and found to agree fairly well with the normal curve.

The Mother's Civil Status. The Child's Sex.

To begin with, an examination has been made to ascertain whether any differences exist touching the length of the period of lactation between unmarried and married mothers in the material or between boys and girls. If such is the case, consideration to this must then be taken in that which follows.

For the period of time b^1 the average length is 4.19 ± 0.108 months for the 447 unmarried mothers and 4.48 ± 0.038 months for the married; the corresponding figures for b+m are 6.46 ± 0.11 resp. 7.11 ± 0.34 months. The difference between the unmarried and married in the former case is statistically probable $(0.29\pm0.11$ months), and significant in the latter case $(0.65\pm0.12$ months). That the unmarried suckle a shorter time than the married mothers in spite of the supervision which is certainly at least as effective for the unmarried as for the married mothers, is no matter for surprise and is an already well-known fact. This is surely in the first place because the unmarried mothers are to a greater extent in employment away from home. However, it should also be pointed out that from many points of view, the material of unmarried mothers is composed in a different way from that of the married mothers. Thus the unmarried mothers

 $^{^{1}}$ In the sequel, in accordance to that stated above, b will indicate the period during which the child was given the breast only, while b \pm m will indicate the period during which the child was given the breast at all.

are on an average, of a lower age (diff. in this material is 3.47 ± 0.28 years), further, their children are to a greater extent first-born. Closer comparisons could not here be carried out owing to the relatively small number of unmarried mothers.

There is hardly any reason for assuming that the sex of the child should have any influence on the length of the lactation period. If the matter is examined within the material as a whole, it is also seen that the difference between the boys and girls is very slight (it does not exceed 0.07 months either for b or b + m), and that it can be a matter of chance. If an examination concerning this question, is also made of the different sections of the material which has been divided into groups according to age of mother and birth number of child and its weight at birth — see below — it will be found that there is certainly a tendency in the boys to a longer b than in the girls in some groups, whereas the case seems to be the reverse applied to b + m, but the differences are slight and may be due to chance.

Age of the Mother.

In order to obtain a uniform material for calculating the effect of this factor on the length of the lactation period, the unmarried mothers have been excluded owing to the fact that they have shown to have different mean values for \mathbf{b} and \mathbf{b} + \mathbf{m} than the married mothers.

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If a rough estimate is first made of the whole material of married mothers it will be seen that there exists a tendency, such as literature information had given reason to expect, in the younger mothers, to have a shorter b + m than the older ones. The differences in the here observed material are not so great which probably is due to the material being controlled (see below). If the limit is drawn at the age of 30 years, no difference can thus be seen in the material, but drawn again at 25 years, it will at least be statistically probable (0.22 \pm 0.86 months).

If, in order to eliminate the possible significance of the child's birth number, we now make a comparision only between unipara of the various ages, it will be seen that the tendency for $b\,+\,m$

to be shorter in the lower ages is still there (Tab. I). For girls the difference between the ages 16—20 on the one hand and 26—30 on the other, is statistically probable (–0.76 \pm 0.27 months). Had the material been greater, it is very likely that the difference might have been proved statistically for the whole material of first-born children.

 $\label{eq:Table I.} Table\ I.$ Period b+m. Married mothers' first-born children.

Age		Boys	Girls				
of mother	amount	$M \pm \varepsilon(M)$	amount	$M \pm \varepsilon(M)$			
16-20	65	6.98 ± 0.29	43	6.62 ± 0.25			
21 - 25	335	$\textbf{6.98} \pm \textbf{0.12}$	300	7.06 ± 0.11			
26-30	422	6.99 ± 0.11	408	7.88 ± 0.10			
31—w	274	7.18 ± 0.12	267	7.16 ± 0.18			
16-ω	1 096	7.08 ± 0.06	1 048	7.18 ± 0.06			

If the figures for the same material for b only, are studied there will however be seen a tendency in exactly the reverse direction (Tab. II). Here it appears as if b were longer in the younger mothers than in the older ones. The differences are slight and cannot be statistically proved on this relatively small material. The tendency is however manifest and pervades both in boys and girls.

The same relation between the younger and elder mothers concerning b and b + m is again met with if one examines the matter in the children that are not first-born. The material is too small to provide full evidence, but the course of the figures within the age classes are the same as in the first-born children, both for b and b + m.

It should be added that the weights at birth in the material of those born first resp. those born later, are distributed in the same manner in the younger as in the older mothers, so that this factor can also be considered as eliminated. It would thus appear that the period b independent of the birth number of the child were longer in the younger mothers than in the other ones whereas the reverse obtains for the period $\mathbf{b}+\mathbf{m}$. We shall return to this matter later when discussing the results obtained.

 $\begin{tabular}{ll} \it Table II. \end{tabular}$ Period b. Married mothers' first-born children.

Age	1	Boys	Girls				
of mother	amount	$M \pm \varepsilon(M)$	amount	$M \pm \varepsilon(M)$			
16-20	65	4.52 ± 0.29	73	4.47 ± 0.26			
21 - 25	335	4.49 ± 0.12	300	4.43 ± 0.18			
26-30	422	$\textbf{4.42} \pm \textbf{0.11}$	408	4.42 ± 0.12			
31-ω	274	4.28 ± 0.14	267	4.89 ± 0.15			
16ω	1 096	4.41 ± 0.07	1 048	4.44 ± 0.07			

The Child's Birth Number.

Since it appears that the older mothers have a longer total period of lactation than the younger ones, it is quite thinkable that one cause of this may be that on an average, the children of older mothers have a higher birth number than those of the younger mothers. It is indeed not improbable that the first-born child has a shorter average suckling period than those born later. This question must however be more closely investigated. Since it has previously been shown that the mother's age can play a rôle in the length of the suckling period, also independent of the child's birth number, it is most appropriate to study the influence of the birth number within sections of the material in which the mothers in each are of about the same age. As long as the significance of birth weight in this connection is not known - first born children weigh on an average less than those born later it is also appropriate that all the children within this material belong to the same weight class. In this way irrelevant data which might possibly enter into the calculations can most assuredly be avoided.

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Table III.

Period b. Married mothers.

Age	First-born (I)		Born later (II-w)	
of mother	amount $M \pm \varepsilon(M)$ amount		amount	$M \pm \varepsilon(M)$
	1	birth weight	3 000—3 490	
16-30	618	4.42 ± 0.09	211	4.68 ± 0.17
$31-\omega$	194	4.15 ± 0.17	194	4.56 ± 0.17
	1	birth weight	3 500—3 990	
16-30	521	$\textbf{4.45} \pm \textbf{0.10}$	262	4.79 ± 0.18
$31-\omega$	180	4.16 ± 0.18	273	4.82 ± 0.14

Age of mother	First-born (I)		Born later (II—w)	
	amount	$M \pm \varepsilon(M)$	amount	$M \pm \varepsilon(M)$
		birth weight 3	3 000—3 490	
16-30	618	6.98 ± 0.09	211	7.21 ± 0.14
$31-\omega$	194	7.20 ± 0.16	194	7.41 ± 0.17
		birth weight	3 500-3 990	
16-20	521	7.02 ± 0.09	262	7.30 ± 0.10
$31-\omega$	180	7.16 ± 0.19	278	7.89 ± 0.14

The comparisons between the first-born children on the one hand and on the other hand those born later, are therefore made for the present on a material comprising the married mothers of the ages 16—30 years the birth weight of whose children is $3\,500$ — $3\,990$ gr. It is then to be seen (Tab. III and IV) that the first-born children in this material have an average suckling period that is somewhat shorter than that of those born later. This applies to b (diff. = -0.34 ± 0.16 months) as well as to b + m (diff. = -0.28 ± 0.13 months). Owing to the claims made on its compo- 16-47322 Acta Padiatrica. Vol. XXXIV

sition, the material has become quite small, for which reason the differences are not significant. If instead, the age group over 30 years and other weight groups are selected, one will obtain the same course in the figures as above and differences, of almost the same magnitude which, of course, speaks for the differences being real. No comparisons between the children No 2 and 3 etc. could be made as the material was too small.

The period b as well as the period b + m, independent of the mother's age and the child's birth weight, thus seems on an average shorter in the first-born children than in those born later. These experiences agree with those made by Rudberg who on an uncontrolled material examined by means of a questionnaire, obtained similar results.

The Child's Birth-weight.

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As the mother's civil status and the mother's age as well as the child's birth number, independent of each other, have proved capable of affecting the length of the suckling period, it is most appropriate, for previously given reasons, to examine the possible effect on the latter which the child's birth-weight can exercise within sections of the material in which the influence of the variations of the above-named factors cannot be assumed to prevail.

The examination has for the present, been made on the married unipara of the ages 16—30. The limit has been drawn at the birth weight of 3490 gr. No difference as regards b or b + m is to be observed between the weight group above this limit or below the same. The same condition prevails if the examination is made on pluripara and within the ages over 30 years. The child's birth weight can thus largely be said not to have any influence on the duration of the suckling period. Regarding the extreme weight group under 2500 gr it would appear probable, as might be expected, that the suckling period is longer for b as well as b + m but the number of individuals in this weight class is too small to allow any closer calculations.

Discussion of the Results Obtained.

When judging the results obtained on the material submitted here, one must bear in mind that the feeding of the children has been controlled during the whole time. This of course means that a certain standardisation of the feeding has taken place in so far as the individual wishes and ideas of the mothers have been allowed to prevail to a considerably lesser degree than if it had been a question of an uncontrolled material. In general, it can certainly be said that within a controlled material it relatively more often depends on the ability of the mothers to suckle rather than on their willingness to suckle, and this may well have been the reason that the differences in the length of the period of lactation here shown between certain fractions of the material are rather slight. According to the previously mentioned authors who have pointed out that the elder mothers suckle their children longer as a whole, the differences are considerably greater. The balance which in this respect is thus provided, if the feeding is controlled applies probably above all, to the period of mixed food. On a material in Gothenburg, Wallgren has shown the decisive significance of control for the length of this period. The disadvantage that the differences in a controlled material are small is compensated however by the fact that in such a material one comes nearer the gist of the question, that is the ability of mothers under different conditions to give their children the breast during a sufficiently long period.

It has been seen above that one of the reasons why the older mothers are able to suckle their children a longer time than the younger ones lies in the fact that to a greater extent they are pluripara. This can of course be connected with the circumstance that the suckling technique is worse in unipara but this factor loses in importance the better feeding is controlled from the commencement. There seems no reason to assume that as regards the married women employment away from home should be so much more widespread among the younger mothers or among the mothers with fewer children that this is able to affect the result. Neither improved technique nor employment can therefore

be of probable decisive significance in this connection. It is rather to be expected that the more favourable position of pluripara which has been proved as prevailing independent of age is caused by inner secretional, local anatomical or other factors which here do not permit of any judgement; this view finds support in the parallels which can be drawn with the lactation conditions of domestic animals (see below).

Pure age factors however, evidently also have some effect, independent of the child's birth number, on the length of the total suckling period (b + m). Touching this it is of particular interest to state that whereas the older mothers have a longer b + m, the case is the reverse when a question of the period b only. Involuntarily one gets the impression that the older mothers compensate for their inferior ability to give the breast alone by protracting the mixed food period for a lengthered time. If one studies the period b + m only, which generally seems to have been done formerly, it can convey the wrong idea that the older mothers have altogether better lactation conditions. Actually conditions may be perfectly the reverse. In the latter case, one might expect to find in the material a negative correlation between the periods b and m, that is, a pervading tendency to protract the period of mixed feeding if the period of giving the breast alone is short and vice versa. A calculation also shows that a like joint variation between b and m exists in a pronounced degree in the material (correlation coeff. = -0.56 ± 0.02). The older mothers can thus hardly be said to be more favourably placed as regards lactation in spite of their having an evident tendency to give the breast for a longer period than the younger ones.

In judging the lactation ability of mothers it is of course not sufficient to decide only the length of the period of lactation. Among other factors which must also be considered there is in the first place in this connection, the amount of milk secreted. Unfortunately it is difficult to obtain, from a sufficiently large material of women, such information on the daily milk secretion

 $^{^{1}}$ The calculation is made on 1 000 married mothers selected at random from the material. As the observation period has not extended beyond the child's first year of life, it has been controlled that the period b \pm m in none of these 1 000 cases has exceeded 11 $^{1}/_{2}$ months.

as can be utilised. Instead it may here be of a certain interest to attempt to draw parallels with the conditions in domestic animals. In cattle it appears that the milk production after a short rise during the first 1-2 months after calving, steadily declines month by month, independent of feeding, until the cows go dry. After 10-12 months of lactation, the milk secretion has sunk on an average, by 50 % (great variations, due to heredity and surroundings). Brody, Ragsdale and Turner who have given this information, have also found after examinations of several breeds of cattle that »the course of decline of milk secretion with the advance of the period of lactation may be expressed by the equation of a monomolecular chemical reaction; that is, the percentage decline of milk secretion with the advance of the stage of lactation is constant». It is also a well-known fact that the year's milk secretion after the first calf is less than after the second and that a steady rise is generally observed up to the 5-6-7th calf, when the year's secretion is nearly 30-40 % higher than after the first calf; thereafter a decline sets in.1 The length of the lactation period does not, on the other hand appear to vary in any high degree with the different birth number of the same cow. Naturally one must be very cautious when it is a question of applying experiences made on animals to mankind, but since it is well probable that it is a similar mechanism that starts and maintains milk secretion in nammals, it is not improbable that the above mentioned conditions in cattle should to a certain extent also correspond to those in mankind. This, however as mentioned above, is still an open question.

In conclusion, the result ought perhaps to be mentioned of a rough estimate which is really beyond the range of this treatise but which can serve to illustrate the significance of controlling the feeding of infants. Following the official mortality figures which in part, have been given together with the description of the material, it is easy to reckon that, of the children born living in Stockholm in 1939 and which reached the age of 2 months but which were not registered in the Child Welfare Centres during

¹ I am indebted to Prof. J. Axelsson, Ultuna, Uppsala, for this information.

the year (nearly 25 %), approximately 0.82 % must have died before they reached their second year of life. The corresponding figure for the children registered in the Child Welfare Centres and for which the average registration age can be put at 2 months, is as mentioned before 0.37 %. A direct comparison of this figure with the preceding one can be made and it will follow that the mortality among children over 2 months which were not controlled at Child Welfare Centres is more than twice as high as among the children of corresponding age which have been controlled at the Centres. The figures make no claim to accuracy but they make it evident how very important it is that the children who do not attend the Child Welfare Centres should be traced and supervised. The matter presents a particularly striking contrast if the circumstance is included in the calculation that a great number of the children who have not been registered at the Child Welfare Centres have been controlled by private doctors and that these latter largely belong to the most prosperous classes which also return the lowest infant mortality figures (RIETZ). There is thus a remnant of non-controlled infants among whom mortality appears particularly high. It is not quite out of the question that this high mortality may be connected with the characteristic curtailment of the period of suckling for the uncontrolled children.

Summary.

In order to ascertain the significance of the civil status and age of mother as well as the sex, birth number and birth weight of the child, for her lactation ability the author has made examinations on a material of 4084 infants at the Stockholm Child Welfare Centres as to what degree the duration of the period of lactation varies with the factors mentioned. Consideration has herewith been taken, on the one hand to the period during which the mother has given the breast only (b) and on the other hand to the period during which she has given the breast at all (b \pm m). The results are as follows.

As was to be expected, the unmarried mothers has, in spite of supervision, a shorter b and b + m than the married mothers,

which must in the first place be ascribed to the circumstance that the unmarried mothers to a greater extent, have employment away from home.

The sex of the child could not be proved to have any noteworthy influence either on b or b+m. The same applies to birth weight although in this case the weight class under 2 500 gr probably occupies an exceptional position.

It has formerly been pointed out in literature that the older mothers give their children the breast for a longer period than the younger mothers. A closer analysis of the causes appears not to have been undertaken. The reason for this must partly be that the older mothers are to a greater extent pluripara; as unipara have a shorter b and b + m than pluripara independent of the age of the mother and the weight of the child at birth. But this is not the only cause, as the difference also appears in unipara at least as regards b + m. When it is a question of b only there rules however the reverse condition, here the younger mothers have a longer suckling time throughout. Therefore another cause of the longer total lactation period (b + m) in the older mothers might be sought in the circumstance that the older mothers compensate for their inferior ability to give the breast only by protracting the period of mixed feeding. The view finds support in the correlation calculations made with reference to b and m within the material. The differences in these respects, between the older and the younger mothers in the material are small all round, and smaller than was to be expected by reason of the information given in literature; this surely stands in connection with the fact that the feeding within the material here described is controlled.

Since the mortality among the infants of Stockholm that are not controlled at the Child Welfare Centres appears to be at least twice as great as the mortality among the children of corresponding age that are controlled at the Child Welfare Centres evidence is given of the importance of tracing and supervising the uncontrolled children.

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Der Werdegang einer akuten Myelose bei einem 13 monatlichen Kinde.

Von

CORNELIA DE LANGE.

Es kommt wohl selten vor, dass man die Entwicklung einer akuten Myelose auf den Fuss folgen kann und da unsere Beobachtung ausserdem noch mehrere Besonderheiten aufweist, möge die Veröffentlichung angewiesen sein.

Das Kind A. B. 13 Monate alt, wurde dem Emma-Kinder-krankenhause überwiesen mit der Diagnose: Rachitis, Bronchitis, starker Gewichtsverlust. Die Familienanamnese ist ohne Bedeutung. Das Kind wurde drei Monate an der Brust ernährt. Mit vier Monaten Husten, war aber nicht krank dabei. Sechs Wochen vor der Spitalsaufnahme bekam es Keuchhusten ohne Fieber. Während der letzten Tagen jedoch ist Fieber da und das Kind hat eine Rhinitis bekommen. Obgleich der Appetit erhalten blieb, ging das Körpergewicht bedeutend herunter.

Status praesens bei der Aufnahme am 23.5. 1946. Lebendiges Kind, das nicht der Eindruck macht schwer krank zu sein. Körpergewicht 7 700 g. Die Temperatur der ersten Tage ist eine Continua remittens, Maximum 39°,5. Mässige Rachitis. Drei Zähne vorhanden, Mundhohle ohne Befund, nur die Tonsillen etwas gross. Kleine Lymphdrüsen an den Kieferwinkeln, hinter dem Musculus sternocleido-mastoideus, supraclaviculär, in den Achseln und Leistenbeugen. Herz perkutorisch normal, Herztöne etwas dumpf, über den Lungen bronchitische Geräusche mit etwas verlängertem Exspirium. Die Leber überragt den Rippenbogen um drei Fingerbreiten, die Milz um zwei. Letztere ist

ins besondere nach der medialen Seite vergrössert und hat eine feste Konsistenz. Das Kind ist hypotonisch in Armen und Beinen.

Die erste Blutuntersuchung am 24 Mai ergibt: Hämoglobin nach Sahli unkorrigiert 62 %, rote Blutkörperchen 3 600 000, weisse 33 400, Senkung nach einer Stunde 28 mM. Formel: Stabkernigen 3, Segmentkernigen 32, Lymphozyten 64, Monozyten 1 %. Mässige Polychromasie. Auf 100 Leukozyten ein kernhaltiges rotes Blutkörperchen. Unter den Lymphozyten befinden sich einzelne Exemplare mit dunkelblau gefärbtem Protoplasmasaum. Die Möglichkeit eines *Pfeifferschen* Drüsenfiebers wird erwogen. Die Reaktion nach Paul-Bunnel erweist sich jedoch als negativ, was immerhin im Kindesalter nur eine beschränkte Beweiskraft hat. Es wäre auch möglich die plasmazytoiden, respective lymphozytoiden oder monozytoiden Zellen mit dem vor kurzem durchgemachtem Keuchhusten in Verbindung zu bringen.

Eine zweite Blutuntersuchung fand statt am 28 Mai: Leukozyten 32 000, Jugendformen 3, Stabkernigen 2, Segmentkernigen 45, Myelozyten 1, Lymphozyten 41, Monozytoide Zellen 8 %. Unter den den Lymphozyten zugeteilten Zellen finden sich vereinzelte mit dunkelblauem Protoplasmasaum, die wieder Ähnlichkeit aufweisen mit den von Glanzmann beim Drüsenfieber als Plasmazytoiden benannten Zellen. Auf 100 Leukozyten 2 Normoblasten Mässige Anisocytose und Polychromasie. Die VON PIRQUETSche Reaktion hat sich als negativ erwiesen; eine Diphtheriekultur der Nase (langwährende Rhinitis) und des Pharynx ebenso. Urin ohne Befund. Am 31 Mai zeigen sich beim Kinde Petechien auf beiden Armen und Beinen mit einer gewissen Prädilektion für die Gelenke; es gibt derer jedoch auch auf Brust und Bauch und an der Stirn entsteht ein Hämatom. Die Bronchitis ist jetzt fast verschwunden und die Milz hat bedeutend an Grösse abgenommen. Thrombozyten 210 000. Blutungszeit 11/2 Minute, Gerinnungszeit 31/2 Minuten. Am selbem Tage geht die Temperatur herunter und hält sich während 5 Tage in normaler Höhe.

Mit dem Fieberfreiwerden geht eine bedeutende Besserung des Allgemeinzustands einher; von 6 bis zum 15 Juni jedoch ist die Temperatur wieder leicht erhöht und schon am 4 Juni liess sich feststellen, dass die Milz wieder um drei Fingerbreiten unter dem Rippenbogen hervorragt. Die Leber ist unverändert gross geblieben. Aus einer dritten Blutuntersuchung am 5 Juni geht hervor: Leukozyten 28 000. Formel: Segmentkernigen 39, Eosinophilen 7, Lymphozyten 46, Monocyten 1, Plasmazellen ähnlichen Zellen 7%. Unter den Lymphozyten auffallende Formen, diesmal keine Normoblasten. Am 7 Juni lautet die Formel: Jugendformen 1, Stabkernigen 5, Segmentkernigen 47, Myelozyten 1, Lymphozyten 37, plasmazytoide Zellen und monozytoide 9%. Auf 100 Leukozyten 1 Normoblast.

Aufs Neue verkleinert sich die Milz und ist am 12 Juni nur noch gerade zu palpieren. Am 16 Juni geht die Temperatur auf 36°,1 herunter um im Laufe desselben Tages zu steigen bis 39°,9. Dann kommen 5 hohe Gipfel (Fig. 1) mit einem Maximum von 40°,6. Es liegt etwas vom Typus des Wechselfiebers darin, nur geht an den zwischenliegenden Tagen die Temperatur nicht ganz zur Norm. Das Kind ist schwer krank. Es gibt sehr viel Nasensekret, eine nochmalige Diphtheriekultur ist wieder negativ. Im Harn finden sich vereinzelte Leukozyten, sonst negativer Befund. Das Kind hat jetzt wieder eine Bronchitis und hustet viel. Am 24 Juni überschreitet die Milz den Rippenbogen um 4 Fingerbreiten und bei der Blutuntersuchung werden zahlreiche MalariaTertianaParasiten angetroffen, aber ausserdem hatte sich das Blutbild sehr geändert in einer Weise, die in der Malaria keine Erkläring findet. Das dargereichte Chinin hat das Fieber in so weit beeinflusst, als der Wechseltypus verschwindet, aber bis zum Exitus bleibt Fieber bestehen. Die Malariaparasiten sind, dank sei der Therapie, innerhalb weniger Tagen aus dem Blute verschwunden. Die Milz vergrössert sich immer mehr; am 1 Juli erreicht dieselbe mit einem Auslaufer die linke Crista ilei (Fig. 2). Man kann den Auslaufer in die Hand nehmen und fixieren, sodass eine Punktion sich gefahrlos machen lässt. (Über die folgenden elf Blutuntersuchungen, das Resultat der zweimaligen Tibiapunktion und der Milzpunktion wird in Anschluss an die Historia morbi berichtet werden.)

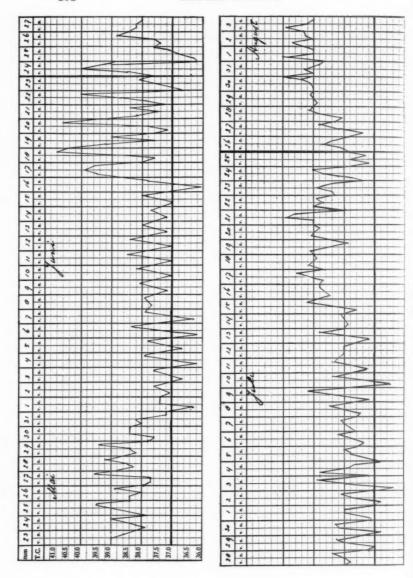




Fig. 2.

Auch die Leber vergrössert sich, es erscheinen wieder Petechien auf dem Bauch (keine Thrombopenie). Die Anämie schreitet fort. Am 15 Juli erreicht die Milz noch immer die Crista ilei. Auch im Gesicht erscheinen Petechien. Am 18 Juli hat der kleine Knabe frequente, schleimige, blutige Entleerungen (Dysenterie und Paratyphus B Kultur negativ). Der Allgemeinzustand verschlechtert sich zusehends. Im Mageninhalt fehlt die freie Salzsäure. An den letzten Lebenstagen ist das Kind blass-cyanotisch und dyspnoisch.

Der Exitus kam am 3 August nach einem Krankenhausaufenthalt von etwas mehr als zwei Monaten. Eine Sektion wurde verweigert; es war jedoch möglich Teile von Milz und Leber zur histologischen Untersuchung zu bekommen.

Die Therapie hatte bestanden in intramuskulären Injektionen von Blut und von Hepatoplex und in dem Genuss von Folin enthaltenden Gemüsen (Salat, Endivien) letzteres weil wir so besonders imponiert waren von den gleich zu erwähnenden Änderungen im roten Blutbilde.

Das Blut. Färbung der Ausstriche mit GIEMSA (da die MAY-GRÜNWALDsche Lösung zur Zeit nicht erhältlich war, konnte nicht panoptisch gefärbt werden) mit der Peroxydasereaktion nach Sato, kombinierte Färbung nach GIEMSA und Sato und mit Pyronin-methylgrün nach PAPPENHEIM. Anfänglich fanden sich nur geringe qualitative Änderungen im Blutbilde bei schon bedeutender Milz- und Leber Vergrösserung. Die beschränkte Zahl von Zellen, die, wie sich später herausstellte, irrtümlicher Weise als lymphozytoide, plasmazytoide und monczytoide in der Nomenklatur von Glanzmann betrachtet wurden und ein Vermuten auf Drüsenfieber wachriefen, sollen hinterher als Myeloblasten aufgefasst werden. Während des ersten Monats im Krankenhause bestand eine leichte Anisocytose und Polychromasie und fanden sich spärliche Normoblasten (1-3 auf 100 Leukozyten), keine Megalozytose. Fortschreitende Anämie, bei der Aufnahme 62 % SAHLI unkorrigiert, kurz vor dem Tode 32 % und abnehmende Erythrozytenzahl. Thrombozyten (9 Zählungen) immer vermehrt, wechselnd von 20 bis 96 %. Einen Monat nach der Krankenhausaufnahme fing die Zahl der kernhaltigen roten Blutkörperchen bedeutend zu steigen an. In der Periode vom 26 Juni bis zum 2 August, das war der Tag vor dem Exitus, vermehrte sich diese Zahl von 19 auf 200 Leukozyten bis auf 105 auf 200, also auf etwas mehr als die Hälfte der weissen Blutkörperchen. Diese Vermehrung fand nicht in einer regelmässigen Weise statt. Anfänglich ging es schnell aufwärts, dann folgte eine temporäre Senkung bis 32 auf 200 Leukozyten. Es entwickelte sich des weitern eine bedeutende Megalozytose. Alle Stufen von Basophilie liessen sich an den Erythrozyten und Erythroblasten beobachten. Nur die Minderheit der Erythroblasten waren Normoblasten mit orthochromen Protoplasma, die Mehrheit hatte stark basophiles und viele gehörten zu den Makroblasten und stellten sehr grosse Formen da mit graublauem Protoplasma. In einzelnen dieser zeigten sich Vakuolen. Viele Erythroblasten wiesen Karyorhexis auf, des weiteren gab es amitotische Kernteilungen und abnormale mitotische. Keine Cabotsche Ringe.

Es blieb immer eine mässige Leukozytose vorhanden; die

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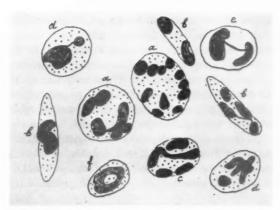


Fig. 3. Pathologische Leukozyten. a. Gigantoleukozyten mit Hypersegmentation. b. Zugespitzte Formen. c. Fremdartige Anordnung der Kernfragmente. d. Bizarre Kernstücke teils ohne Zusammenhang. e. Verlust der Granula. f. Ringförmiger Kern.

höchst gefundene Zahl betrug 80 000 in der Zahlkammer; mit Abzug der kernhaltenden Roten jedoch an diesem Tage nur 67 200.

Das Differenzieren der weissen Zellen hat grosse Schwierigkeiten gemacht wegen der grossen Zahl von Übergangsformen und pathologischen Gebilden. Im Anfang machten die polymorphkernigen Leukozyten weniger als die Hälfte in der Formel aus; später schwankte ihre Zahl immer um die Hälfte. Es gab keine Linksverschiebung, dennoch bestand im Blute kein richtiger Hiatus leukaemicus (wohl aber im Knochenmark), denn im Blute kamen auch Promyelozyten, Myelozyten und Metamyelozyten vor, sei es in beschränkter Zahl. Die neutrophilen wiesen sowohl im Blute als im Knochenmark vielfach pathologische Formen auf, wie Fig. 3 zeigt. (In dieser halbschematischen Skizze sind zu photographischen Zwecken die Zellgrenzen scharf umrandet.) Es gab da erstens sehr grosse Formen, wie man dieselben im Kinderblute auch nach banalen Infektionen antreffen kann. Diese grossen Formen zeigten meistens auch eine Hypersegmentation. Dann hatten die Kernfragmente fast immer ihre zierliche Konfiguration verloren, sie waren plump geworden und der Unterschied zwischen oxyphiler und basophiler Kernsubstanz war verloren gegangen. In mehreren Zellen war die Kernsubstanz ringformig gelagert. Öfters enthielten Zellen zwei Kernfragmente von sehr verschiedener Form und Grösse entweder mit einem dünnen Strang verbunden oder los von einander liegend. Dann noch gab es viele Zellen, die als polymorphkernigen zu identifizieren waren, aber ihre Form völlig geändert hatten, längliche, an beiden Enden zugespitzte Gebilde. Man könnte behaupten, dass diese Zellen Kunstprodukte seien entstanden beim Ausstreichen des leicht lädirbaren Blutes. Ich will das nicht gänzlich abstreiten, muss aber sagen dass dieselben öfters nicht in der Streichrichtung lagen, sondern quer darauf. Schliesslich kamen Leukozyten vor, an den Kernsegmenten erkenntlich, die ihre Granulation fast oder ganz verloren hatten. Letzteres ging auch aus den Satopräparaten hervor.

Basophile Leukozyten wurden nicht angetroffen, eosinophile vereinzelt.

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Die zweite Rubrik enthält die Myeloblasten und die von NÄGELI beschriebenen und in seinem Lehrbuch abgebildeten Paramyeloblasten mit ihren Merkmalen. Die Zahl derselben wechselte bei den Zählungen von 21/2 bis 18 %. Es ist sehr wohl möglich, dass in diese Gruppe beim Differenzieren vereinzelte sehr grosse Makroblasten mit basophilem Protoplasmaleib hineingeraten sind, denn die Unterscheidung war dann und wann sehwierig. Das möge einem fremd vorkommen, wenn man jedoch die Abbildungen dieser Zellen in verschiedenen Lehrbüchern der Hämatologie mit einander vergleicht, so wird man sehen, dass dieselben einander öfters täuschend ähnlich sind. Im Satopräparat zeigt ein Teil dieser grossen Zellen eine positive Peroxydasereaktion, die aber quantitativ sehr verschieden ist in den verschiedenen Zellen; ein Teil derselben, die allerjüngsten sind negativ. Einmal sah ich einen Myeloblast der ein rotes Blutkörperchen phagozytiert hatte.

Promyelozyten waren vorhanden in $3-7\frac{1}{2}\%$, Myelozyten in 2-7%, Metamyelozyten in 3-15%. Die Myelozyten und Promyelozyten zeigten öfters einen eingebuchteten Kern und in

einigen Promyelozyten gab es abnorme Kernteilungsfiguren. Schwierig war oft der Unterschied zu treffen zwischen einem Metamyelozyten und einem Myelozyten mit eingebuchtetem Kerne und zwischen Metamyelozyten und abnormen Leukozyten.

Eine folgende Rubrik in den Zählungen enthält in 9-21¹/₂ % »kleine Zellen» und umfasst Mikromyeloblasten, Paramikromyeloblasten, kleine Lymphozyten und wahrscheinlich auch mehrere Normoblasten mit schmalem, basophilem Protoplasmasaum und nackte Erythrozytenkerne. Falls man sich auch hier wieder wundert über die ungenügende differentielle Diagnostik, sei es erlaubt hinzuweisen auf die Abbildungen 2 und 3 pathologischer Mikromyeloblasten Seite 208 des Nägelischen Lehrbuchs, 5 Auflage, auf die Abbildung eines basophilen Normoblasts Fig. 27 der farbigen Tafel in der Inauguraldissertation von G. M. H. VEENEKLAAS, Utrecht 1938, auf die eines kleinen Lymphozyten, Fig. 4, Tafel 6, aus dem Leitfaden der Blutmorphologie von Lydia SCHUDEL und die eines Mikromyeloblasten aus derselben Arbeit und schliesslich auf die Abbildung eines kleinen Lymphozyten Plate 2 aus dem »Clinical Atlas of Blood Diseases» by Piney and WYARD. Diese genetisch ganz verschiedenen Zellen sehen einander auf den Abbildungen täuschend ähnlich. Im Peroxydasepräparat zeigt ungefähr die Hälfte dieser »kleinen runden Zellen» eine positive Reaktion, diese kann man also als Mikromyeloblasten respective als Paramikromyeloblasten betrachten, obgleich eine negative Reaktion diese Zellarten noch nicht ausschliesst, gibt es ja auch Mikromyeloblasten und Paramikromyeloblasten mit negativer Reaktion!

Was die mit ziemlich grosser Sicherheit als Lymphozyten zu betrachtenden Zellen betrifft, so kamen die grossen Formen mit azurophilen Granula, die man sonst konstant im kindlichen Blute findet, nicht vor. Es ist möglich, dass einige Male Lymphoblasten von mir zu den Myeloblasten gerechnet worden sind, denn auch hier kann die Unterscheidung eine recht schwierige sein. Öfters sah man kleine Lymphozyten auf einer oder auf beiden Seiten zugespitzt, was wahrscheinlich ein Kunstprodukt war. Die Zahl der als Lymphozyten rubrizierten Zellen (also derjenigen nicht gehörend zur der Kategorie von »kleinen Zellen») betrug 2 bis 14 %.

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Ganz vereinzelt wurden Monozyten angetroffen, zweimal ein Megakaryozyt (keine im Knochenmark).

Einzeln sei hier noch die Formel gegeben vom 2 August, des Tages vor dem Tode: polymorphkernige Leukozyten, öfters mit Hypersegmentation der Kerne 52 %, Myeloblasten und Paramyeloblasten 10,5 %, »kleine runde Zellen» 18,5 %, Promyelozyten 4,5 %. Myelozyten 4 %, Metamyelozyten 5,5 %. Lymphozyten 4,5 %, Monozyten 0,5 %. Die verschiedenen Zählungen haben nicht das Ansteigen einer bestimmten Zellgattung gezeigt, das Bild war immer im Wechsel begriffen.

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Es wurde zweimal eine Tibiapunktion vorgenommen, am 22 Juni und am 5 Juli. Die Punktionen wiesen eine myeloide Transformation des Marks auf. Reife Myelozyten waren selten, ebenso Pro- und Metamyelozyten. Hier gab es also ein Hiatus leukaemicus. Auch hier fiel es wieder schwer, Mikromyelo- respective Paramikromyeloblasten, kleine Lymphozyten und kleine basophile Normoblasten von einander zu unterscheiden. Bei der Peroxydasereaktion hatte man den Eindruck, dass die Mikromyeloblasten etwas grösser waren als die beiden anderen Zellgattungen. Bei der Färbung nach PAPPENHEIM (Methylgrün-Pyronin) zeigten sowohl die grossen ungranulierten Zellen als die obengenannten »kleinen Zellen» ein rotes Protoplasma; diese Färbung konnte also keine Hilfe in der differentiellen Diagnostik sein. Sowie im Blute, blieb auch im Marke ein Teil der grossen Zellen bei der Peroxydasereaktion negativ, d. h. die allerjüngsten Formen. In den positiv reagierenden Zellen war die Zahl der blauen Granula eine sehr wechselnde.

In den beiden Punktaten wurden 500 weisse Zellen gezählt und die kernhaltigen roten Blutkörperchen, welchen man dabei begegnete. Dies war 28,3 % bei der ersten Punktion und 11 % bei der zweiten. Beide Zahlen fallen noch innerhalb der Norm für dieses Alter, obwohl erstere hochnormal ist. Als die erste Punktion vorgenommen wurde, gab es nur vereinzelte kernhaltige rote Blutkörperchen im Blute, zeitens der zweiten 70 per 200

weisse Blutzellen. Auffallend war aber, dass Makroblasten und kernhaltige rote Blutkörperchen mit Kernteilungsfiguren in weit grösserer Zahl anwesend waren als normaliter, wo die Normoblasten in diesem Alter etwa 80 % ausmachen.

Es geht hier um die Frage, ob die Erythroblastose nur ein Streben war, die Anämie auszugleichen, oder ob eine richtige Wucherung des präexistenten erythropoetischen Marks vorgelegen hat. Es ist etwas ganz gewöhnliches, dass man bei der myeloiden Leukämie kernhaltige rote Blutkörperchen im Blutstrom findet. Von Debré, Lamy und Thieffry wird aber die Zahl von 4 bis 6 Normoblasten auf 100 Leukozyten schon eine bedeutende genannt. Diese Werte werden in unserem Falle weit überschritten. NÄGELI behauptet, dass in den Fällen von Luce² und Treadgold³ mit exzessiv hoher Erythroblastenzahl im Blutstrom, eine richtige Wucherung des präexistenten hämopoietischen Marks da war. Ich kann dem für den Fall Treadgolds nicht beipflichten. Diese Beobachtung betraf einen Knaben von 131/2 Jahren und wurde veröffentlicht unter dem Titel: »myeloid Leukaemia in a child with Blood picture of socalled megaloblastic Anemia». Vom Knochenmark wird gesagt: the marrow was myeloblastic and showed few red cells. Die Beschreibung der histologischen Milzund Leberstruktur ist nicht ganz klar, dennoch meine ich, dass hier eine extra-medulläre Hämatopoiesis bestanden hat. Im Fall Luces war die starke Erythroblastosis nur temporär, auch hier bietet das Verständnis der Organmicroscopie Schwierigkeiten, da damals (1903) die Auffassung der Genese verschiedener Zellarten eine ganz andere war, als die heutige. Es kommt mir vor, dass in der Milz keine extramedulläre Blutbildung war, dass dieselbe aber in der Leber nicht ganz fehlte. Dies ist in so weit von Interesse, als Rohr behauptet, dass kernhaltige rote Blutkörperchen nicht in den Blutstrom gelangen können, weil ihnen eine eigene Bewegung fehle: sie müssen daher aus extramedullären

¹ R. Debré, M. Lamy, St. Thieffry, Archives de Pédiatrie. T. III, Nr. 2, 1946.

² H. Luce, D. Archiv f. klin. Med. 77, 2150, 1903.

³ C. H. TREADGOLD, The Lancet. I, 94, 1913.

Herden stammen. v. Buchem und Botman¹ auf Grund klinischer und pathologisch-anatomischer Untersuchungen jedoch behaupten, dass obiges nicht gilt für die Normoblasten, sondern nur für die unreiferen Formen. Wie aus unserer Untersuchung hervorgeht, beteiligen sich Leber und Milz wieder an der Blutbildung, was bei dem jugendlichen Alter des Kindes nicht Wunder nehmen kann.

Die Milzpunktion

wurde am 22 Juli vorgenommen; an diesem Tage enthielt 70 Erythroblasten auf 200 weissen Zellen. Punktat befand sich eine bedeutende Zahl kernhaltiger roter Blutkörperchen, worunter mehrere mit Karyorhexisfiguren, jedoch auch mit amitotischen Kernteilungsfiguren, viele, kleinen Lymphozyten ähnlichen Zellen, aller Wahrscheinlichkeit nach in bedeutender Menge den Mikromyeloblasten angehörig, weiter viele grosse Myeloblasten und Paramyeloblasten, öfters mit eingebuchteten Kernen und schliesslich zahlreiche grosse Kernschollen, welche sich an mehreren Tagen auch im Blute fanden. Diese Schollen bestanden aus einem degenerierten leptochromen Kerngerüst bisweilen mit einem noch erhaltenen hellblauen Protoplasmaflarden. Über die Art dieser Zellen lässt sich nichts mehr aussagen. Kracke² gibt besonders schöne Abbildungen von den GUMPRECHTschollen, die er »smudge cells» nennt und meint, dass ein Teil derselben an den blauen Vakuolen noch als Myeloblasten erkenntlich sei.

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Histologische Untersuchung von Leber und Milz.

Färbung der Schnitte mit Hämatoxylin-Eosin, Eisenfärbung nach Turnbull-Hueck, Färbung nach Domenici, Peroxydasereaktion in Gefrierschnitten.

Leber. (Fig. 4.) Die Blutkapillare sind erweitert und die Leberbälkehen an mehreren Stellen auf einander gedrungen. In

¹ F. S. P. VAN BUCHEM und TH. BOTMAN, Nederl. Tydschrift v. Geneeskunde 83, 4022, 1939.

PROY R. KRACKE, Diseases of the Blood. 2. Ed. 1941.

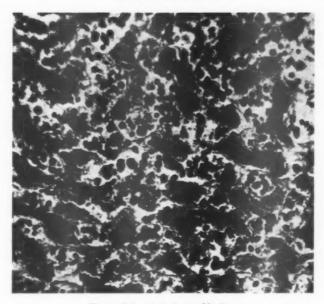


Fig. 4. Leber bei akuter Myelose.

den Kapillaren findet sich eine grosse Zahl kernhaltiger Elemente. Ein bedeutender Teil dieser gehört zu den kernhaltigen roten Blutkörperchen mit vielen Karyorhexisfiguren. Ihr Protoplasma ist fast immer basophil. Man unterscheidet weiter die polymorphkernigen Leukozyten und viele kleine Zellen mit dunklen Kern. Die Mehrheit letzterer weist mit der Peroxydasereaktion eine positive Reaktion auf. Des weiteren gibt es eine bedeutende Zahl grosser Zellen der myeloiden Reihe angehörend und die teilweise mit der Peroxydasereaktion positiv reagieren. Es fällt auf, dass stellenweise in einer Kapillarbucht sich ein Häufchen dieser grossen Zellen befindet, als sei dort eine Brutstelle. Auch periportal gibt es eine bedeutende Zellinfiltration, worin sich grosse Zellen, aber in der Mehrheit die kleineren Formen befinden.

Die Eisenreaktion ist in der Leber praktisch negativ.

Milz. Die Milz weist vereinzelte kleine Blutungen auf. Von Follikeln sind meistens nur Reste vorhanden, jedoch gibt es auch noch gut erhaltene Exemplare. Es gibt eine myeloide Transformation der Pulpa, wobei es auch wieder trifft, dass an einzelnen Stellen die grossen Zellen in Häufchen oder Strängen zusammen liegen. Die Peroxydasereaktion zeigt sich an vielen kleinen und grösseren Zellen positiv. Des weiteren findet sich in der Pulpa eine grosse Zahl kernhaltiger roter Blutkörperchen.

Auch in der Milz ist die Eisenreaktion praktisch negativ.

Rekapitulieren wir jetzt die wichtigsten Pünkte unserer Beobachtung.

- Der Werdegang dieser akuten Myelose konnte fast vom Anfang bis zum Ende verfolgt werden.
- Als schon eine sehr bedeutende Milz- und Lebervergrösserung vorlag, wies das Blut zwar eine mässige Leukozytose auf, aber noch fast keine qualitativen Veränderungen.
- 3. Die Grösse der Milz war anfänglich sehr wechselnd.
- Die Milz erreichte einen sehr bedeutenden Umfang, was gewöhnlich bei der akuten Myelose nicht der Fall ist.
- 5. Es gab eine ungewöhnlich starke Erythroblastämie, die aller Wahrscheinlichkeit nach nicht als eine Wucherung präexistenten Markgewebs zu betrachten ist, sondern als eine Reaktion auf die Anämie, an welcher Reaktion sich die extramedulläre Hämatopoiesis beteiligte.
- Die polymorphkernigen Leukozyten wiesen mehr Veränderungen auf, als gewöhnlich wird angegeben.
- Als Verwicklung trat eine Malaria tertiana auf, welche den Blutstatus nicht merklich änderte, und keinen Konnex aufwies mit der wechselnden Milzgrösse.

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FROM THE TOWN AND COUNTY HOSPITAL, SVENDBORG (CHIEF SURGEON: V. REINSHOLM, M. D. CHIEF PHYSICIAN: W. THUNE ANDERSEN, M. D.)

DENMARK.

Lethal Hereditary Bullous Epidermolysis.

Survey — and a Typical Case.

By

JØRGEN LENSTRUP.

The term hereditary bullous epidermolysis comprises some morbid pictures which are characterized by vesicle formation in the skin with subsequent exfoliation of epidermis, and by familial occurrence, but which differ from one another, for example by varying pathologico-anatomical findings and different heredity.

 $Bullous\ hereditary\ epidermolysis$ thus comprises three different, though kindred affections:

- 1) Simple bullous epidermolysis (simple mechanical bullosis (Siemens) (keratolysis bullosa)) is a very benign hereditary skin affection. It presents a great tendency to formation of vesicles in the skin after mechanical injuries, the separation of the vesicles merely giving rise to superficial wounds which heal completely and rapidly without formation of scars. A microscopic examination of the vesicles discloses that they form in the very epidermis (Siemens), the horny layer alone exfoliating, whence the affection really ought to be termed bullous keratolysis. The deeper layers are not involved, nor is there any change in the quantity of elastic fibers. The affection is dominantly hereditary (Siemens). In a few families, however, it is reported to have been found with recessive heredity (Cockayne).
- 2) Dystrophic bullous epidermolysis (dystrophic mechanical bullosis (Siemens)) likewise is a congenital skin affection with a good prognosis quoad vitam, but with changes involving much

greater depths. Here, too, the vesicles appear after mechanical injuries. They do not occur on the skin alone but also on the mucous membranes. The bullae separate and leave profound skin defects, which heal slowly and under formation of large scars and atrophic areas with pigmentation and small milliary cysts. The nails are involved, and often present disturbances of growth or are quite absent; dental changes may also occur and, very seldom, bone defects too. The vesicles form between the epidermis and corium. There is found edema of the cutaneous cells and of the tissue round the corium papillae, the number of elastic fibers being reduced considerably. The cutaneous vessels are dilated and surrounded by cell infiltration. The affection is inherited recessively (SIEMENS).

GILLIS HERLITZ has drawn attention to the circumstance that, even though the two skin affections described present similar features, which render it warrantable to parallel them under the term hereditary bullous epidermolysis, they cannot by any means be regarded as different forms of manifestation of the same disease. The two affections are different with regard to appearance, location, dissemination and healing as well as to difference of heredity.

3) Lethal hereditary bullous epidermolysis is by GILLIS HERLITZ set up as a third affection in this group. This affection is characterized by familial occurrence of the tendency to bulla formation in the skin and on the mucous membranes with subsequent separation of epidermis or of the uppermost mucous layer, manifestation already at birth, initially malign tendency, and always lethal issue. The disease presents several points of similarity with dystrophic epidermolysis, such as, for example, the kind and location of the vesicles, the nail changes etc., whereas it distinctly differs from it by its malignity, the extensive congenital skin defects, the frequent bone dystrophies, and the healing without cicatrization, skin atrophies or pigmentations. Moreover, it is mentioned that milliary cysts have not been met with in this disease.

Touraine divides the epidermolyses somewhat differently. He mentions (a) an *epidermolyse bulleuse simple (dominante)*, which quite corresponds to (1) simple bullous epidermolysis. In

my opinion, Touraine's (b) Ȏpidermolyse bulleuse hyperplastique (dominante)», in which the bullae may be both superficial and profound, appearing both on skin and mucous membranes, leaving hyperkeratoses, atrophies and isolated milliary cystes, ought to be included in the aforementioned scheme of (2) dystrophic bullous epidermolysis. The disease is reported to be of dominant heredity however. Perfectly corresponding to (1) dystrophic bullous epidermolysis, Touraine further describes (c) an »épidermolyse bulleuse polydysplasique (récessive)». As sub-division thereof Touraine describes a »forme maligne ou léthale» which must be assumed to be identical to that affection which, as was motivated above, ought to be set up as an independent disease, namely, (3) lethal hereditary bullous epidermolysis.

Lethal hereditary bullous epidermolysis.

According to GILLIS HERLITZ lethal hereditary bullous epidermolysis must be assumed to be simply recessive; theoretically, however, it may be of a more complicated recessive kind. It must be reckoned with that the disposition may arise by mutation in different families, and thus manifest itself in a child which is homozygote in that respect.

The children are often born with extensive epidermal defects or with large vesicle formations in the skin. Without any definite traumatic etiology, new bullae constantly appear on skin and mucous membranes. The nails are involved, often separated. The skin is very vulnerable, Nikolsky's symptom (separation of the horny layer by a single firm passing with a finger) is present. The skin defects heal without atrophy or scar formation. The bones of affected fingers and toes may be involved so that single phalanges are atrophic. Atrophy of teeth may also be found.

In the recorded cases the children have perished in the course of a few weeks or months, mostly without it being possible to demonstrate the cause of death proper.

In a good many cases it is impossible to provoke vesicle formation by pressure. Therefore it is doubtful whether it may be reckoned with that the bullae arise without preceding trauma, it

being remarkable that they are mostly located to regions which are the most exposed to traumata, namely: hands, elbows, legs, occiput. The congenital epidermal defects are chiefly located to the legs, which may probably also be assumed to be the most exposed to traumata through intra-uterine movements.

Histological changes.

As is well-known the skin consists of the following layers:

	(the horny layer	stratum stratum	corneum lucidum
Epidermis		stratum	granulosum
	stratum germinativum (Malpighian layer)	stratum	
Corium	stratum papillare stratum reticulare		

Tela subcutanea.

In the described cases the bulla formation was found over or in the Malpighian stratum germinativum. In some cases separation of the horny layer alone was described, whereas the Malpighian stratum germinativum was found to be edematous with scattered necroses or quite atrophic, in other cases the horny layer was found to be separated together with the Malpighian layer, the entire epidermis thus being exfoliated.

In some cases parakeratosis and hyperkeratosis were found. Slighter hyaline changes of the corium were mentioned.

The sweat glands are scantily developed in the atrophic skin. Frequently they merely consist of small, simple loops, but sometimes they look quite normal.

The sebaceous glands are by some authors reported to be degenerated or quite lacking. The hair follicles are atrophic or described as being the seat of folliculitis.

In the majority of descriptions it is mentioned that the blood and lymph vessels are enlarged, the capillaries are dilated, plethoric, and encircled by cell infiltration consisting of lymphocytes and plasma cells. Bartels, on the base of these findings, sets up the theory that bullous epidermolysis may conceivably be a primary vascular affection. In my opinion it is more reasonable to regard the vascular dilatation and the cell infiltration as a simple, unspecific inflammatory reaction to the cutaneous necroses.

Microscopy of the normal-looking skin did not disclose anything pathological. Gillis Herlitz reports, however, that in one of his cases he has observed that the epidermis on apparently normal skin is separated from the layer below. This change may, however, be thought to have occurred during sampling or preparation, such an exfoliation, as mentioned before, easily taking place (cf. Nikolsky's phenomenon).

When the skin subsequent to affections is healed, a well-developed epidermis is found. The corium papillae are retracted, and the Malpighian stratum germinativum may be edematous with indistinct cell boundaries in the basal layer.

In elastin-stained preparations several authors find a reduction of the elastic fibers. The elastic tissue beneath the vesicles is sparse, being in one place described as being »in körnigem Zerfall» (in granular decomposition). It is alleged that, in the intact skin, the elastic fibers may be lacking in stratum papillare, whereas, in the depth, they are found in normal quantity. In the skin healed after affections the number of elastic fibers has likewise been found to be reduced, particularly in the uppermost sections of cutis.

Other authors have not been able to find this reduction of the elastic tissue. Schroder & Wells, on the contrary, mention in their case: »Elastic fibers were concentrated and apparently more numerous in all layers in the more atrophic skin sections.»

Wells describes slight toxic changes in the myocardium, liver, spleen, and kidney. Other writers have not been able to demonstrate affections in the organs.

Writer's Case.

Annie, born 9/11-1946, died seven months old.

Parents healthy, not related by blood. No skin affections in the family, no similar cases known in the family. The mother had received no medicamina in her pregnancy which had run a normal course, nor did she present any symptoms, particularly no signs of syphilis, the Wassermann reaction being negative. Five older brothers and sisters are healthy.

The birth took place at home, normally, without difficulties, in the I. cephalic presentation; the waters passed during the parturition. Immediately after birth the child cried lustily. Weight 3 000 g, length 50 cm. The placenta is reported to have looked quite normal, the membranes too. Immediately after birth the child was hospitalized.

On admission, she is found to be born at full term. Both legs present extensive epidermal defects involving the anterior and medial surfaces of the feet and legs, extending upwards to the middle of the left leg and a little above the right knee. Some of the toes (left big toe, 2nd and 4th toes, right big toe) which are involved in the affection (e) are shrunk and atrophic as compared to the remaining normally coloured toes. The affected toes are without nails, whereas the nails of the normal toes are well developed with free borders. In the affected regions the epidermis is separated (a few remains about to be exfoliated), corium thus presenting itself dark-red, in some places almost black, rough, not bleeding spontaneously but easily injured (b). In some places the tissue is retracted, particularly on the heels. The affection is sharply delimited from the surrounding skin (c) which looks quite normal.

Both feet present maximal dorsal flexion (f) so that they lie along the anterior surface of the legs, where the toes form distinct irregular impressions (g). They can be replaced up to a little beyond a right angle. The blood circulation seems to be normal.

The examination of the child does not otherwise disclose anything particular. She is a little delicate but not exactly poorly, sprawling lively, breathing normally.

Course.

Already on the day after the child's admission large bullae appeared in the inguinal folds, and next day several bullae ap-



Fig. 1. Affections on the legs four days post partum.

- a: Fresh bulla, sharply delimited from the surroundings, tense, with thin wall, containing clear fluid.
- b: Denudated, uneven, slightly retracted corium with slight hemorrhages.

c: Sharp delimitation against the surrounding normal skin.

d: Incipient healing of a section which, three days before, had had the same appearance as b.e: Involved atrophic toes without nails, among which one quite unaffected toe.

f: Prominence of calcaneus.

g: Impression formed by left big and second toe. A quite similar, though somewhat less pronounced impression is seen on the right leg. peared on previously perfectly normal-looking skin. Thus, on the fifth day, a typical bulla appeared just beneath the left knee, as is seen in Fig. 1 (a). In the same picture it will be observed that the defective skin sections are healing rapidly (d), for they dry up at first and are subsequently covered with a new, thin layer of epidermis issuing from the periphery. The areas thus healed on the right leg presented themselves at birth just as the still denudated area round the right instep (Fig. 1, b).

Subsequently, new bullae continued to form. They were of varying size, measuring up to several centimeters, roundish, tense, covered by a thin, horny layer, but still translucent, sharply delimited from the surrounding, normal-looking skin. The underlayer is not indurated. When the single element has formed, it does not enlarge but new elements continue to appear. The vesicles develop in the course of a few hours, rupturing soon afterwards, leaving the subjacent layer of skin dark-red, running, and bleeding at the slightest injury. During the subsequent days the area dries up and is slowly covered by thin epidermis.

After some time the skin has quite the same appearance as the surrounding skin. Bullae may appear on perfectly normal-looking skin. They do not arise on the denudated areas, but they sometimes appear on areas which are healed after previous affections.

The defects which are seen after ruptured vesicles quite resemble the denudated areas observed immediately post partum. The borders of the areas being tattered, as if there had been bullae, it may probably be assumed that those areas have been the seaf of vesicles ruptured antenatally or at birth.

The liquid content of the vesicles is light, clear, yellowish, thin. Cultivation on ascitic agar, blood agar, and broth fails to give growth.

The vesicles preferably appear in places where the skin is exposed to wear: Legs, buttocks, nape, elbows, sucking-finger. Vesicles rapidly appear on the tongue and palate, thus making it difficult for the child to drink. These affections heal rapidly and do not recur for some time, forming again, however, in bad periods.

Everywhere the skin is very vulnerable. Nikolsky's symptom

is very pronounced. It is impossible to provoke bulla formation by pressure.

During the subsequent months new bullae continued to appear — in some periods there were many, in others but few — but resisting all treatment. The skin of the legs gradually healed entirely with the exception of an area round the right knee which, already at birth, was strongly retracted and the seat of profound necrosis. The healed areas presented neither pigmentations nor cicatrization.

The bulla formation was during the time preceding death very considerable, the child finally presenting denudated areas measuring up to 8 or 10 cm both on the nape, flanks, and other places. Finally there appeared moreover milliary, granuliform, cystoid formations here and there.

During the whole course the child's general condition was bad; she did not thrive and, after seven months, weighed no more than 4 650 g. When the dressings of the wounds were changed, she was greatly distressed, crying and restless, physically and psychically inferior. She did not try to grasp objects which were held up before her, nor did she fix her gaze on them. Horizontal nystagmus gradually developed. Ophthalmoscopy revealed that both eyegrounds were somewhat atrophic with blurred papillary borders.

The roentgenogram of hands and feet after ten days did not present anything abnormal. Nor did the bones of the hands after the lapse of four months present anything abnormal, whereas the feet presented lacking bone formation corresponding to the ungual phalanges of the second and third toes of the right foot and the medial phalanx of the little toe of either foot.

During the whole course of the disease the toes originally involved were smaller than the others, but there was no progressive atrophy.

The remaining examinations did not disclose anything particular. The temperature, apart from a few subfebrile periods, was normal during the course. During the last days the temperature rose to about 40° (104° F.). The child presented no meningeal, pulmonary, gastro-intestinal or other symptoms. No signs of secondary infection in either bullae or wounds. Finally the temperature rose to 41.6° (106.8° F.), and then death ensued.

Treatment.

The ruptured vesicles were for a time brushed with a 2 % silver nitrate solution. That treatment not being tolerated, the wounds were merely covered with cloths soaked with paraffin oil. Paraffin oil was also used for cleaning the skin. Moreover, lucosil ointment was tried; and, to allay the pain on changing the dressings of the wounds, nupercainal was applied. Epicutan powder afforded no improvement. Bathing with potassium permanganate solution aggravated the condition.

During the first days alphasol mixture was given (sulfonamidothiazole preparation) but without effect. Moreover, on account of the desiccation, steam and saltwater 0.9 % subcutaneously, which were tolerated without discomfort. She was nursed at breast for some time, then fed cow's milk and water. She received 10 000 units of vitamin A and 6 000 units of vitamin D a day, shock treatment with 600 000 units of ultranol D, 10 cg of ascorbic acid a day, becoplex for some time, besides 15 cg of nicotinamide a day.

Pathologico-anatomical findings.

On autopsy, the lungs showed strong hyperemia and, in some places, slight edema, but no signs of pneumonia or other inflammatory changes. The other organs presented slight acute stasis but otherwise no changes.

Microscopy of one of the toes, which on the roentgenogram presented lacking ossification of the ungual phalanx, disclosed normal cartilage anlage with normally developed joint surface. The ossification has just commenced and is not nearly so far developed as in the other toes, although it seems to run a normal course. There is no nail anlage. The toe in question was involved in the original profound affection of the feet, thus obviously preventing ossification. Microscopy of another toe, which was the seat of fresh bulla formation but which had not previously been affected, disclosed normal development of the phalanx.

The pathologico-anatomical changes in the several preparations of the skin are evident from the illustrations. The prepara-

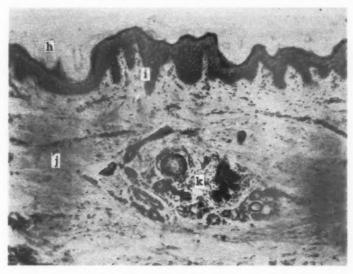


Fig. 2. Unaffected skin.

h: Normal horny layer.

i: Well-developed corium papillae, normal cells in stratum germinativum.

 Normal structure of the connective tissue of corium. No inflammatory changes.

k: Small and slightly developed hair follicles encircled by not surely changed sebaceous glands.

tions were also stained for elastin. Thereby normal development and distribution of the elastic fibers were found in the non-affected skin, whereas the elastic tissue of the healed skin was somewhat sparse in the upper layers corresponding to the existing atrophy of the skin, the quantity of elastic tissue in the profounder layers being perfectly normal, however. Therefore it is scarcely to be assumed that the reduced number of elastic fibers is a primary feature of the affection, but that it is rather to be regarded as a simple consequence of the atrophy of the skin.

In sections from the tongue the epithelium is seen to be separated entirely from the tip of the tongue whose surface is covered with leukocyte-infiltrated exudate. The remaining mucous membranes are not affected. It should be noted that the affected mu-

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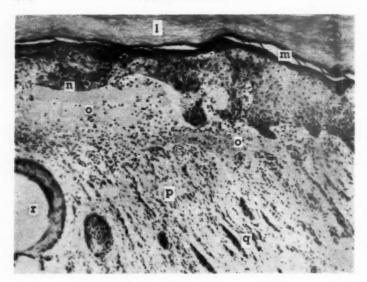


Fig. 3. Skin from the border of a fresh bulla.

- l: Horny layer.
- m:Stratum corneum (horny layer) separated from stratum germinativum by faintly eosinophilic acellular exudate (here but little pronounced more so in other sections).
- n: Stratum basale, from which the corium papillae are retracted, stratum germinativum the seat of cell infiltration.
- o: Exudate which raises the epidermis from corium and, farther towards the left, entirely separates the layers under formation of bulla. The exudate reaches a little beyond the centre of the picture. It contains polymorphonuclear leukocytes and red blood corpuscles.
- p: Edema of corium with some infiltration of polymorphonuclear leukocytes, lymphocytes and plasma cells continuing a little beneath the surrounding non-affected epithelium. No eosinophilia.

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- q: Somewhat enlarged, congested capillaries indicating hyperemia. No fibrinoid degeneration.
- r: Cavity lined with stratified squamous epithelium which thrusts off horny masses towards the lumen (see also u and x),

cosa regions (palate and tongue) are derived ectodermally. Changes in the endodermally derived mucosae were not found here — nor have such probably been described before.

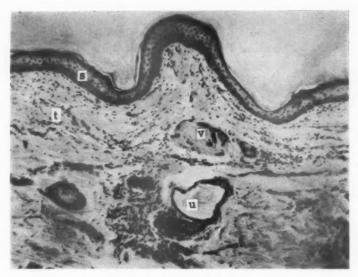


Fig. 4. Skin from healed affection.

s: Low, somewhat atrophic epidermis, no corium papillae.

t: Slight infiltration of lymphocytes; elastic tissue destroyed (preserved in deeper layers).

u: Horny cyst (corresponding to r and u) in immediate connection with hair follicle. Such cysts are frequent in preparations from healed affections.

v: Squamoid, eosinophilic masses surrounded by giant cells.

The development of the changes.

As will be seen on comparing the preparations, a bulla is formed by extravasation of fluid in the uppermost layer of corium so that the epidermis is raised from corium (a, o). At the same time the horny layer (1) tends to be separated from the stratum germinativum (m). Thus the whole epidermis is thrust off, leaving the hyperemic, slightly bleeding corium (b, p, q), which is rapidly covered by a new thin atrophic layer of epidermis (d, s), in which the corium papillae are almost undeveloped. In the course of the disease hyperemia with formation of edema and emigration of cells (p, q) is observed, which subsides during healing, however.

The development of the sebaceous glands is normal; nor do 18*-47322

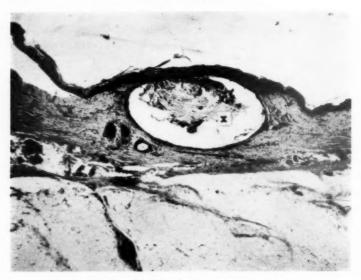


Fig. 5. Skin from healed affection (lesser magnification).
x: Horny cyst just as r and u, but so big that, macroscopically, it presents itself on the surface of the skin as a miliary cyst.

they present anything special apart from their naturally being plainer and reduced in number in the healed atrophic skin.

Sure hyperkeratoses are not seen.

Even on normal skin the hairs are badly developed (k).

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As was mentioned, several small milliary cysts (r) have in this case appeared particularly at the termination of the course of the illness. They have developed in connection with hair follicles (u), issuing from them or, most probably, from sebaceous glands. They are frequently seen in skin from a healed process (u), where they sometimes attain macroscopic size (x). Gillis Herlitz has not in his cases found such small cysts; he mentions on the contrary that, in this disease, the affected regions heal without formation of miliary cysts. Schroder & Wells in their cases report eystic degeneration of sebaceous glands and publish a microphotograph which distinctly shows a cyst issuing from a sebaceous gland and partly containing secretion from the sebaceous gland. Thus the

appearance of these cysts is somewhat varying, probably depending on how profound the affections are.

It is worth mentioning that those cysts are found in the skin at the same time as the bullae. The cysts develop from a rudimentary primordium of hair or of sebaceous glands, and they contain scales, which may possibly give rise to sensitization of the whole skin to its own epithelium, whence the affection may be regarded as allergic. In my opinion this hypothesis is refuted by the absence of other allergic manifestations, such as, for example, eosinophilia.

The atrophic skin, moreover, presented some squamoid masses (v) lying superficially in proportion to the cyst. They probably represent remains of atrophic hairs. They are surrounded by giant cells which must be regarded as the expression of a simple foreign body reaction.

The vessels (q) in the fresh affection are somewhat dilated and congested, but otherwise they do not present anything particular. The hyperemia probably is a mere inflammatory reaction and no primary feature of the affection.

I wish to express my indebtedness to Dr. Harald Olesen, of the Pathological Institute of Fyns Stift (Fionia Diocese) in Odense for much helpful criticism and advice.

Summary.

Lethal hereditary bullous epidermolysis is set up as one of the affections in the group of epidermolyses parallel with simple and dystrophic epidermolysis. It is characterized by bulla formation and epidermolysis with subsequent healing without cicatrization, with frequent bone dystrophy and ungual changes, rapid lethal issue, and familial occurrence. A typical case is described and illustrated. Already at birth the patient presents large epidermolyses. There is found bulla formation beginning with edema and cell infiltration in the uppermost layer of corium. The epidermis is exfoliated and replaced by a new thin atrophic epidermis, with corresponding imperfect development of sebaceous glands and elastic fibers. Hairs and sebaceous glands are atrophic everywhere and, after exfoliation of the epidermis, in further decomposition.

In contradistinction to some previously reported findings, milliary cysts form from sebaceous glands. Cultivation from bullae yields no growth. The affection is resistant to any treatment applied. New bullae continue to appear, and after seven months the child dies without signs of infection. Fig. 1 shows the macroscopical look of the affection, whereas Fig. 3 illustrates the typical microscopical changes in the skin.

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si of cl no tie FROM THE CHILDREN'S CLINIC OF THE MUNICIPAL UNIVERSITY AND THE PATHOLOGIC INSTITUTE OF THE BINNENGASTHUIS, AMSTERDAM.

Prognosis in Sympathoblastoma.

By

S. van CREVELD, M.D. and R. van DAM, M.D.

In October 1939 a girl, aged 18 months, was admitted to the Children's Clinic of the Municipal University of Amsterdam. Since birth she had had a swollen abdomen. During the first year of life there had been no complaints, but then gradually the girl made a less healthy impression. She was the first child of healthy parents; during pregnancy the mother had not been ill. The child was spontaneously born in due time; birth-weight about 2 750 grams. Growth and development normal during the first year of life, and with the exception of chicken-pox at the end of this year, the girl had not been ill.

In the hospital the development of the girl proved to be normal and in accordance to her age. She did not so much make the impression of being ill, as of suffering. The feeding condition was moderate. The senses were normal. Mouth and throat no particularities. Thoracic organs normal. The abdomen was greatly swollen, and did not move at respiration. There was a clear net of veins visible on the pale wall of the abdomen. The umbilicus was slightly protruding. At palpation the abdomen was rather taut and deep pressure seemed to cause pain. At the right lateral side below the slightly enlarged liver a round tumor of the size of a tangerin could be palpated; it was of firm consistency and clearly confined especially below and at the medial side. No abnormal swelling of glands. Reflexes, urine, faeces and sedimentation rate of the erythrocytes normal. Blood picture: leucocyte count 9 600, with a moderate shift to the left; no anemia. Blood-

platelets count somewhat diminished. — Blood sugar content in fasting condition, urea-, chlorine- and sodium-content of the serum normal. Takata-Ara test negative. Blood pressure normal. Von Pirquet's test negative. Roentgenograms of skull, lungs and wrists no peculiarities. Some liver- and kidney tests were normal. After perabrodil-injection the pyelogram showed at the left side a fairly normal pyelum, at the right side a very large pyelum greatly divergating laterally. After introducing a contrast clysma, on a survey-roentgenogram of the abdomen the colon at the right side appeared to be pressed downward.

On account of these findings the probable diagnosis of hydronephrosis was made, either a primary one, or a secondary one caused by pressure on the ureter. The tumor below the liver was considered to be the right kidney, which was pushed from behind by a tumor. — In view of the age of the child and the absence of alarming symptoms it was decided, in agreement with the urologist (dr. VAN CAPPELLEN) to assume an attitude of expectation and to control the child regularly.

Three months later, in Jan. 1940, the girl was admitted for the second time. Her weight had somewhat diminished; the general condition had remained fairly good and there were no special complaints. Of late the tumor had somewhat grown. Also now no anemia, dyspnoea, cyanosis or edema were present. Respiration normal. No abnormal swelling of glands. Also the thoracic organs showed no peculiarities. The abdomen was somewhat swollen, especially on the right side. In the right upper part of the abdomen a superficial tumor could be palpated with a smooth surface, about 9 × 6 cm, from the right lateral side to the medial side. Under this tumor a large tumor of firm consistency could be felt, which in the right medio-clavicular line was reaching till about 2 cm below the level of the umbilicus; the border in the medial direction could not be palpated. The urine now and then contained some albumen and some erythrocytes. The sedimentation rate of the erythrocytes was normal. In performing the ascending pyelography (dr. VAN CAPPELLEN) on the right side a very large pyelum was found, reaching far into the lateral direction. Now we decided to operate, after a preceding irradiation.



Survey of the abdomen after a contrastclysma. At the right side the colon is pushed downward.

After three roentgen-irradiations within 13 days the size of the tumor had not diminished. The girl did not look well, took her food without appetite and her weight was steadily decreasing.

On operation on Febr. 20, 1940, dr. VAN CAPPELLEN found in the right renal region an inoperable tumor, firmly grown together with the under-layer. Many vessels were running over the tumor. When a small part of the tissue was removed for histological examination a hemorrhage arose, which could be stopped only with difficulty. The report of the pathologist was: tumor tissue, constructed of a thin connective tissue stroma with connected groups of small round cells. These cells consist of a nucleus very rich in protein, nearly without protoplasma. Polymorphia almost absent; some splitting of the nuclei. The pathological diagnosis thus was: small cellular roundcell sarcoma. After the operation no roentgen-therapy was applied. The prognosis was considered to be unfavorable.

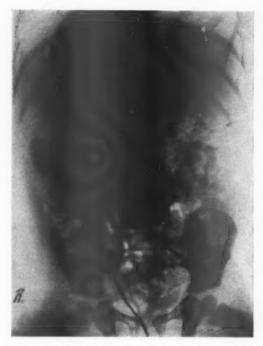
About $1^{1}/_{2}$ year after the operation the girl came to the outpatients department of the Clinic in excellent condition; she had greatly gained in weight. The cicatrix of the operation was good. In the abdomen a tumor of the size of a tangarin could still be palpated. No anemia, urine normal.

 $2^{-1}/_2$ years after the operation: no complaints; the child was quite well. The tumor still had the same size.

4 years after the operation: all was well, and no tumor could be felt.

5 years after the operation, in Dec. 1945, the girl was controlled again. She had grown well and in the abdomen no tumor could be felt. Urine normal. The intravenous pyelogram showed at the right side a somewhat deformed picture of the kidney and pyelum; at the medial side of the kidney a small calcarious shadow was visible.

This quite unexpected course of the disease caused us to reexamine the slides of the tissue, removed at the operation in 1940. We found the following histological picture: it is a tumor, consisting of small round or oval cells with nuclei rich in chromatin, and only poorly developed protoplasm. On examination of the type of the cells by means of the oilimmersion-lens many cells appear to have offshoots. The cells are lying amidst a fine-fibrous medium, mostly poorly developed, sometimes slightly better visible. Moreover in many places areas with only a few or no nuclei are found, in which areas a dense network of extremely fine fibres is present, around which the cells are lying more closely together. In the van Giesonslides these small fibres have a yellowish colour. For



Ascending pyelography at the right side: Very coarse pyelum (condition in Jan. 1940).

the greater part they are lying in the form of a network, sometimes they are running in parallel lines. It is a tumor rich in vessels, where the cells are close together, at first sight without much order, but on further examination it appears — apart from a pseudo-alveolar order and the above mentioned bands around the areas rich in fibres — that there is evidence of forming forces: the cells are inclined to lie in rows and in small circles. On account of this picture we thought to be justified in modifying the original diagnosis into the one of sympatoblastoma.

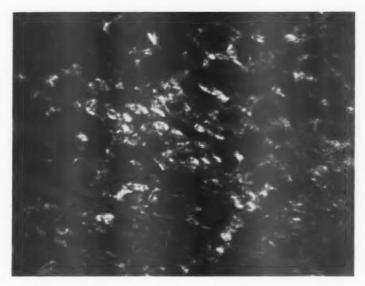
In view of this modified diagnosis the course of the case becomes somewhat less incredible, but it remains sufficiently remarkable to report here.



Intravenous pyelogram. At the right side a somewhat disfigured pyelum, Medially of the kidney a small calcareous shadow (condition in Jan. 1946).

This type of tumor at first considered to be a small-cellular "congenital sarcoma" (PARKER 1880), was recognized by Schilder as a neuro-ectodermal tumor and regarded as a glioma (1909); finally Wright (1910) on account of the resemblance in structure with the embryonal construction of sympathicus and adrenal marrow, conceived it to be a neuroblastoma.

By comparing the degree of maturation of the cells with the normal embryonal development of the sympathicus and adrenals, during the next years various classifications have been made. They all are based on the scheme of POLL who laid down the three degrees of development of the sympathetic nervecell in the fol-



Area rich in fibres amidst the tissue rich in cells of sympathoblasts.

lowing order: sympathogonia, sympathoblast, ripe sympathetic ganglioncell, while next to these out of the sympathogonia also the chromaffin system is developed. Thus we can differentiate between sympathogonia, sympathoblastoma and sympathetic ganglio-neuroma (Pick 1912, Landau 1912, Herkheimer 1917 and many others).

Our case is an example of a typical sympathoblastoma. Landau is of the opinion, that this type should be counted among the exquisitely malignant tumors, on account of the histological picture as well as of the frequent metastases. However, we must not forget that many of the cases described in literature do not represent a pure type; in the majority of cases there is more or less a propensity to maturation. Fischer in 1922, using the data from the literature, has fixed all possible transitory forms and degrees of maturation in a rather complicated scheme. From this theoretically speaking we may expect the occurrence of sympatho-

blastomae which histologically are completely in agreement with the dreaded malignant type, but which nevertheless will develop into a ripe form, so that the expected consequences do not happen. We think to be justified in interpreting our own case in the same way. Is this really a case of a tumor of originally malignant nature? Or is it possible that the same histological picture holds true for a benignant and a malignant type? No speculation can answer these questions. Anyhow we have to reckon with the possibility that some rests of unripe cells remain, which in a certain constellation may cause a renewed growth. We have reason to assume that such surprising turns in sympathoblastomae are not quite rare.

In 1927 Cushing and Wohlbach gave the history of a boy in whom at the age of 2 years an inoperable paravertebral tumor had been found; the histological diagnosis, made by Ewing, was "a malignant tumor, which might very well be a sarcoma" and the possibility of endothelioma or neurocytoma was considered. According to the illustrations the picture is completely in agreement with that of our slides. Also this boy recovered but ten years later, on account of a remaining paraplegia, laminectomy had to be carried out; then from the spinal cord some tissue was removed which at histological examination appeared to consist of completely differentiated ganglioncells, with capsule cells and neurilemma cells. Thus a sympathetic neuroblastoma may be the predecessor of a ganglioneuroma.

Roussy, Huguenin, Perrot and Laracino (1941) even report a case of abdominal sympathoma, which after extirpation produced a recurrence on the other side and afterwards, with intervals, gave many metastases. Part of these disseminations disappeared after irradiation, part of them spontanously. Some years after the first examination the patient's condition gradually ameliorated.

Fèvre, Lamy and Baudoin (1943) saw in a baby the occurrence of multiple tumors of the skin, originating probably from a tumor of the scrotum. One of these metastases, removed from the corner of the eye, was recognized by Oberling as being a sympathoblastoma. The explosive dissemination lasted for a period of

five months; after that all tumors gradually disappeared without leaving a trace. The authors have cited an analogous observation by Debré c. s.

In the older literature cases of multiple subcutaneous sympathomae have been described by KNAUS (1898) and by KREDEL and BENCKE (1903).

At the meeting of the American Pediatric Society in 1940, FABER communicated that out of 40 young patients, in whom a certain diagnosis of sympathetic neuroblastoma had been made on account of findings at biopsy or at autopsy, after 3 till 8 years ten were still alive. In some of them metastases had occurred. The treatment had consisted of the total removal of the tumor, the partial removal of the inoperable tumor with or without subsequent roentgenologic treatment or of the extirpation of the primary tumor with irradiation of the metastases.

From these data in the literature it appears, that our case is not a single one and that in practice the prognosis of the sympathoblastoma need not absolutely be hopeless.

Summary.

A girl of nearly two years old had a tumor in the right renal region, which after the findings at operation and the result of the histological examination provisionally was regarded to be a sarcoma. An unfavourable prognosis was given. However, five years later the general condition of the girl was excellent and no tumor could be felt in the abdomen. This gave reason to reexamine the old slides and it appeared necessary to modify the former diagnosis in that of sympathoblastoma. The prognosis of this sympathoblastoma is discussed, in consideration also of a number of publications on this subject. The conclusion is drawn that this prognosis need not be absolutely unfavourable.

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CASE REPORT

FROM THE DEPARTMENT OF PEDIATRICS OF THE ST. JOHN'S HOSPITAL IN ZAANDAM.

Alopecia universalis congenita and hypoplasia renum in a Newborn.

By

TIELINE A. E. JANSSEN (Zaandam) and W. KOX (Zaandijk).

The combined occurrence of two congenital anomalies, each of which has been already described in a number of cases, seemed to render a publication of our case worth while.

In a previous paper (1) it was pointed out that the lanugo is normally shed shortly before birth, and that the casting of the primary hair is followed by the secondary coat of hair. Congenital baldness may be the result of a disturbance in the earliest development of the hair (3—4 fetal month), or in the development of the secondary coat of hair (2). Associations have been found of alopecia universalis congenita with dental defects and defects of the nails. In cases of so-called »major ectodermal defect», moreover, the sweat and sebaceous glands are lacking (3).

Case history.

DIRK was born 31.5. 1944, in "Ons Verpleeghuis", in Koog-aan-de-Zaan, and died six days after birth. He was the first child of a woman who suffered from malaria. His father was a healthy man. There had been no abortions. The child was born three weeks prematurely with a birth-weight of 2 000 grammes. No asphyxia. At first he did well. 3.6. 1944, he cried with a hoarse voice. The next day there were numerous hemorrhages in the skin, especially in the folds of the skin. The diapers contained blood, and when the infant sneezed sanguis appeared from the nose. It was striking that the child was absolutely hairless. There was no lanugo hair, nor did he possess any eye-brows or eye-lashes. The nails did not show any abnormality. The skin was dry and wrinkled,

that of the soles of the feet had thickened and presented rhagades. There was edema of the hands in a slight degree. There was »snuffles» without secretion. Internal organs without anomalies. Normal body temperature. Body-weight 2 kg.

Luetic infection was excluded. It was not possible to make a more extensive examination as the child died soon after his admittance to the St. John's Hospital in Zaandam.

Autopsy, 34 hours post mortem, by Dr. H. VAN DER FLIER. (Pathological Laboratory of the Wilhelmina Gasthuis in Amsterdam: Professor Dr. H. T. DEELMAN).

S. 44301. The main points are given here.

Body of a small child with numerous hemorrhages on hands, feet, round the anus and on the back. No rhagades. The child is absolutely devoid of hair.

Panniculus adiposus 3 mM., fat whitish-yellow. Muscles well developed, reddish-brown, glassy.

Diaphragma 4th intercostal space. The liver reaches 2—3 cM. below the costal margin. No anomalies of omentum, peritoneum or intestines. Some cubic centimeters of transudate in the abdominal cavity.

The lungs have collapsed. Pleura parietalis normal. Thymus rather small, glassy on section. Pericardium normal and containing some transudate.

Heart: 11 grammes, the size of the child's fist, firm consistency, the apex formed by the left ventricle. Epicardium with many petechiae and larger bloody spots. Heart-muscle light red-brown, firm, the wall of the right and the left ventricle being equal in thickness. No anomalies. The foramen ovale and the ductus BOTALLI are still open.

Lungs: normal configuration, marked emphysema. On section greyish-red hue. On pressure air and mucopus escape from the bronchi of the left upper lobe. There is some lung edema. Nothing abnormal in pleura visceralis, main bronchi, hilus glands and hilus vessels.

No abnormalities of the trachea, aorta, tractus digestivus, mesenterium, gall-bladder and bile ducts, genitalia interna, bladder and columna vertebralis.

Spleen: 4 grammes (normal 5 $^1/_2$ —6 $^1/_2$). Firm consistency, normal appearance. On section a few follicles visible.

Pancreas: normal in form and size.

Liver: 105 grammes (normal 75—100), rather firm-elastic with a sharp anterior border. Capsule without anomalies. Smooth surface. The vena portae is empty. On section: tough consistency, colour brown-yellow-red, it resembles somewhat the colour of a flint liver. In some

spots the connective tissue has slightly increased. There are also some protruding, not sharply defined, spots the size of a pin's head (gummata or partial fatty degeneration of the liver).

Adrenals: normal in shape and size. Some petechiae on the surface. On section: broad brownish-yellow cortex, medulla very hyperemic.

Kidneys: 2 1/2 grammes (normal 15-20). The fat- and connectivetissue capsules are removed easily. Smooth surface. On section: thin, pale brown, well-marked cortex. Cortex and medulla well-defined, ratio 1-4. The medulla does not protrude, is well marked, brown-red. Pyelum and ureter are normal.

Microscopic investigation.

Lungs: slight degree of atelectasis and of emphysema. Some alveoli contain scales.

Heart: without anomalies.

Spleen: idem.

Pancreas: In some spots there is an infiltration with lymphoid cells in the interstitium. Hyperemia in a slight degree, and a very few small hemorrhages. After Levaditi method no spirochetes.

Liver: Cloudy swelling of the liver-cells. Some of the venae centrales have somewhat widened. In the central parts there is now and then dissociation of liver-cells. Here and there wide spaces of DISSE. Some infiltration with lymphocytes round Vv. centrales; in the portal canals infiltration with lymphocytes and leucocytes. Myeloid foci practically lacking. No spirochetes.

Adrenals: Extensive hemorrhage, especially in the medulla, but also in the cortex. No spirochetes.

Kidneys: Smooth surface. Normal glomeruli. The tubuli have sometimes widened. In the medulla many tubules are still embryonic in shape. There is neoformation of glomeruli. The vessels, even those directly under the capsule, are remarkably large and have a thick wall, thus resembling vessels in a more adult stage.

Conclusion: The kidneys represent severe developmental distur-

bances. Marked hyperemia.

As a section of the brain was not possible, we are left in ignorance as to the hypophysis and the regio hypothalamica, which areas are often rightly or wrongly accused as being causative factors in the most widely different diseases, and also in cases of disturbances in the ectodermal development.

Discussion.

In our case we have to deal with a developmental disorder of an organ of ectodermal and one of mesodermal origin.

It may be remarked that the microscopic abnormalities in the kidneys do not resemble those which are found in renal dwarfism.

It is to be regretted that no microscopic investigation was made of the skin. Otherwise it might perhaps have been possible to preclude, or to state, a so-called *major ectodermal defect*. Also a X-ray picture of the jaws post mortem might have yielded interesting information as to the development, or lack, of dental *Anlage*.

As to the cause of death we opine that this may have been uremia. The hemorrhages probably were of the same origin, though it is possible that they were the result of another cause of hemorrhagic diathesis.

In the literature stress is laid upon the fact that atrichia totalis is often a familial disease. Now, it is of some importance that the family history of our case is absolutely negative as to alopecia congenita in any form, and that the second child of the parents, which was born in August 1945, is quite normal.

We did not succeed in finding any example in the medical literature of the combined occurrence of alopecia universalis congenita and hypoplasia renum.

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K R O N P R I N S E S S A N L O V I S A S B A R N S J U K H U S, 30 P O L H E M S G A T A N, S T O C K H O L M

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A C T A P Æ D I A T R I C A





On Brachyoesophagus.

By

ERIK WAMBERG.

The term brachyoesophagus indicates a congenital malformation consisting of an abnormally short oesophagus and a partial thoracic stomach. The junction between the two (cardia) in such cases lies in the thoracic cavity.

Among congenital oesophageal malformations, atresia with or without oesophago-tracheal fistula has long been considered the most common. In 1930 the number of known cases was 231 against only 12 of brachyoesophagus - mainly proven by autopsy. In 1931 FINDLAY & KELLY reported 9 new cases, all diagnosed by oesophagoscopy. At the same time they gave a detailed description of the syndrome and the oesophageal findings. Their observations were soon confirmed by others, and an increasing interest was displayed in this »new» disease. During the subsequent years a number of — mostly American — case reports were published (JACOB, TWEEDIE & NEGUS - CLERF & MANGES - MONKHOUSE & MONTGOMERY - POLLEY) and followed by similar publications from England (BRIGGS & DICK -MYLES), France (LELONG, AIME, AUBIN & BERNARD - LELONG, LAMY & AIME), Holland (BOEVE - GERLINGS), and recently from Scandinavia (HARALD CHRISTIANSEN - WILKEN JENSEN), bringing the number of cases up to a figure of around 70.

Therefore it is, not unjustly, maintained by a few authors that the disease is by no means as rare as ordinarily assumed — perhaps it is one of the most common oesophageal anomalies. Still, several cases have no doubt received an erroneous diagnosis

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(most often that of diaphragmatic hernia) and others have remained undiscovered because of lacking technique in the X-ray examination.

This peculiar anomaly has been mostly dealt with by otolaryngologists and radiologists. Since it is, however, a question of a congenital malformation, appearing in most cases during the first months of life, its diagnosis and treatment as a matter of course fall within the scope of pædiatrics.

During recent years 4 cases have been observed at the Queen Louise Children's Hospital, and therefore it seems warrantable to report the case histories in connexion with a brief survey of the clinical features of this particular disease.

Case History I: A. L., born Apr. 14, 1934. Case Rec. 69/37 & 835/44. Girl, aged 10. Has been suffering from periodical vomiting since birth. The vomiting has not changed in character during all these years, it always occurs during meals, the vomitus is often blood-tinged, but never contains old particles of food. During latter years the vomitings have often been preceded by an increasing pressure feeling behind the sternum, and during the last 6 months there has often been pain in the same site during as well as after meals. No actual dysphagia. Periodical weight loss, thus amounting to 7 kilos during the last year.

Since the age of 4 months hospitalized 5 times, including a stay of 6 months in this department in 1936. The diagnosis was: Oesophageal spasm and hysteria. X-ray of the oesophagus demonstrated one contrast shadow, the size of a walnut, above the cardia, merging with the stomach and another similar shadow on a level with the bifurcation of the trachea. The two shadows were connected by an area, 3—4 cm in length and as thick as a lead-pencil. The changes were interpreted as oesophageal stricture, possibly malformation.

Re-admitted in June 1944. During the stay she had numerous vomitings, increasing in frequency during the first month, usually in connexion with meals. Once a bloody vomitus was brought up, followed by melaena. During the last months of her stay in hospital she had only occasional vomitings and put on weight. To start with she was kept mainly on a fluid diet and given ample water to drink after each meal. Could later tolerate a full diet. — This time X-ray revealed a considerable dilatation in the upper three-fourths of the oesophagus. The lower one-fourth was shaped like a funnel, ending downwards in a walnut-sized hernia-like dilatation extending up through the diaphragm. (Fig. 1 & 2.) Apart from these changes, interpreted as a cardiospasm in a too short oesophagus, two of the films revealed a projection, presumably



Fig. 1. Case I. Dilatation of upper part of oesophagus. Thoracic stomach distinctly visible. Cardia indicated by the arrow.

a »niche», as large as half a pea, at the medial border of the oesophagus. A control examination 2 months later revealed a somewhat slighter dilatation, whereas the hernia-like dilatation and the »niche» were undemonstrable.

Since discharge from hospital in September 1944 the patient had been feeling well, vomiting once in a while, until she was taken ill again in July 1945 and remained so for several months. During this period there were frequent vomitings, almost after every meal, and sometimes dysphagia too. — Now she is feeling perfectly well, she is eating ordinary food and gaining weight.

Case History II: I. L., born Apr. 14, 1934. Like her twin sister (Case I) she had been suffering from vomiting ever since birth. Said to have vomited after every meal during the period of lactation. All the same she throve well. No exacerbation of the condition occurred when



Fig. 2. Oblique view of same case.

she began to have solid food, and the vomitings decreased considerably during the first years of life. She has been hospitalized twice (as a baby and again at the age of 9) without the cause of the disease being discovered. The affection has remained practically unchanged, but the symptoms have never been as severe as in the case of her sister. She only had a single vomiting at several weeks' intervals and never suffered from protracted *bad spells*. No dysphagia, no pain, and no blood in the vomitus.

An ambulant X-ray examination in September 1944 revealed a moderate dilatation in the upper three-fourths of the oesophagus with tapering of the latter 3 finger-breadths above the diaphragm. Between this site and the stomach there was a smooth canal, 3—4 cm in length and as thick as a slate-pencil, which remained completely unchanged. The changes were interpreted as a brachyoesophagus, possibly with a beginning spasm in the cardia.

Case History III: J. K., born March 18, 1940. Case Rec. 661/40 & 194/41. Girl, aged 5. During the first months of life she vomited brownish matter and 3 days prior to admission in 1940 she had had »black vomitings». During the first days of her stay in hospital she had occasional blood-tinged regurgitations and blood in the fæces, later no regurgitations or vomitings, but still occult blood in the fæces. Hæmatological examination revealed nothing abnormal apart from a slight anæmia. On passing a stomach tube down the oesophagus, a resistance was felt 16—18 cm from the incisor teeth. In addition to an 8 hours' retention of the contrast meal in the stomach, repeated X-ray examinations showed a contrast shadow above the stomach and insufficiency of the cardia. It was impossible to decide between hiatus hernia and a too short oesophagus.

Feeling well after discharge, but there was still a positive benzidine reaction in the fæces. — Re-admitted at the age of 11 months. Had no difficulty in taking fluids, but vomited when given mashed potatoes. During the stay in hospital there was some difficulty in eating, as the patient appeared to strain while taking the first mouthfuls. She could not be induced to eat mash, sieved food, or porridge. She had varying, but not daily vomitings. Weight loss of 700 grammes in the course of 3 weeks. — A stomach tube passed down the oesophagus met an insurmountable resistance 21 cm from the incisor teeth, and X-ray examination revealed a tapering below a dilatation of the oesophagus 3—4 cm proximal to the cardia. It was impossible to arrive at a definite diagnosis, but an oesophageal spasm was considered most probable.

On re-examination 6 months later the child was in good health. She had gained 3 kilos in spite of constant vomiting of solid food.

Case History IV: O. P-B., born Febr. 13, 1937. Twin. Boy, aged 8. Vomitings since he was a few weeks of age. During the first months of life only occasional vomitings (about once weekly), most frequently in the morning and several times during 1 hour. In spite of this he throve excellently. When he began to have solid food, the vomitings became more frequent, but could usually be avoided, if all his food was sieved. Admitted to the Fuglebakken Children's Hospital at the age of 11 months after having swallowed a piece of orange which was, however, ejected spontaneously. After a thorough X-ray examination a diagnosis of brachyoesophagus was made. (Fig. 3 & 4.) Later he was oesophagoscoped twice (at the age of $1\,^1/_2$ and 3 years respectively) in Stockholm. In the interval bouginage was tried, but without success.

During the subsequent years he had bad spells at irregular intervals, vomiting several times daily for a few weeks. The amount of vomitus was small, extremely slimy, sometimes blood-tinged, but not acid smelling. On the whole the syndrome did not change in the course of time.

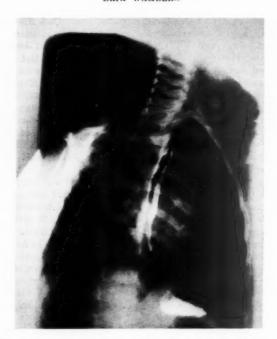


Fig. 3. Case IV. Picture resembling Fig. 1, but the dilatation is less marked.

Two—three years ago hæmatemesis twice and 1 year ago occult blood in the fæces for a couple of months, presumably in consequence of a complicating oesophageal ulcer. Never pain. Now he is feeling perfectly well, is eating all kinds of food normally, but has to masticate thoroughly and drink large amounts of water at each meal. The weight is normal.

Etiology.

The anomaly must be interpreted as a result of incomplete embryologic development. On the other hand there does not appear to be agreement as to its origin. Bund's theory is in brief that a persistence of the right pneumato-enteric recess produces a hernia in which the stomach forms the hernial contents. (This recess is one of the 2 peritoneal extensions issuing from the omental

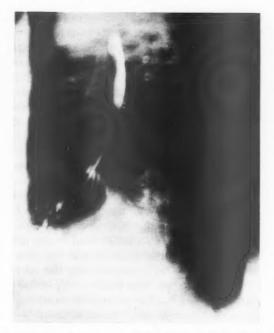


Fig. 4. Lateral view of same case. Folds of mucosa distinctly visible in the thoracic stomach.

bursa and communicating with it. In early foetal life they envelop the oesophageal anlage. The left one gradually disappears, whereas the right one is usually cut off on a level with the diaphragm and persists throughout life in the form of a bursa, the size of a florin, between the oesophagus and the upper side of the diaphragm.)

TONNDORF, who in several ways has disproved this theory, advances another — and apparently more probable — explanation: In the 4th—5th foetal week there is a caudal shift of the diaphragm and abdominal contents which at that time are situated far to the cranial side. In consequence of the growth of the thorax and the traction through the diaphragm which is attached to the oesophagus, the latter will increase in length.

In case this increase in length fails to occur for some reason or other, a major or minor portion of the stomach will remain in the thoracic cavity, whereas the diaphragm, completing its caudal movement influenced by the growing thorax, envelops the thoracic stomach in a thin layer of connective tissue. When the diaphragm later acquires its musculature, a ring of muscles will be formed around the stomach on a level with the normal diaphragm.

Pathology.

Post-mortem examinations and oesophagoscopy have revealed that the junction between the oesophagus and the thoracic stomach is about 14—30 cm from the incisor teeth, varying according to the age of the patient, but usually on a level with the 7th thoracic vertebra. This junction may be in the shape of a thin annular membrane with a small perforation, or else a small fold may project from a greater or lesser part of the circumference. In other cases there will be a gradual reduction of the lumen extending over about 1 cm (varying from $^{1}/_{2}$ —2 cm), making the stenosis tunnel-shaped. The constriction is often concentric (unlike cicatricial strictures) with a lumen of about 4—9 mm.

Distal to the stenosis the mucous membrane is of the same aspect as a normal gastric mucosa, and on microscopical examination it reveals an architecture just like the latter. Therefore there is no doubt that this is a question of a partially thoracic stomach.

No reference to heredity is made in the accessible literature, but familial occurrence has been observed by MYLES and CLERF & MANGES. Among the writer's patients the 2 were twin sisters.

Symptomatology.

The anomaly may remain symptomless throughout life, although that is exceptional. In the great majority of cases it will be disclosed by vomitings. Infants exhibit persistent daily vomitings or regurgitations, either immediately after birth or at the age of a few weeks. Sometimes the vomitings do not begin

until the baby starts having solid food. Cases have been reported in which the vomitings began as late as the age of 4 years.

The vomitings, which may be periodical, nearly always occur during meals, and the food is returned without effort. The amount varies, the consistency may be purely alimentary, slimy, or even blood-tinged. Hæmatemesis has been observed in cases of a complicating peptic ulcer of the oesophagus. (In a few cases, however, they must be interpreted as a sign of incarceration (HARALD CHRISTIANSEN).) On account of the persistent vomitings, one may encounter pseudo-constipation and dehydration. The condition will rapidly disturb the growth of the child, the more seriously the younger the patient.

In the course of the first year the vomitings usually subside, so that the bad periods may occur at several months' intervals. In case of improvement within the first months of life, the vomitings often recur when the baby starts having solid food.

Older children may display dysphagia. They tolerate fluids well, but take solid food in small portions which they masticate thoroughly and swallow with large amounts of water. The vomitings may be preceded by a feeling of discomfort and nausea. Sometimes these children complain of pain, usually arising during or immediately after meals. This pain is of varying intensity and nearly always localized behind the lower part of the sternum. A few authors have reported intensification of the pain in the recumbent position and improvement when the patient sat up or lay on his right side, but this is no doubt a question of an isolated phenomenon. In addition to the symptoms already mentioned, there are other less important ones which in most cases are met with in adults only: pyrosis, cough, dyspnoea, nocturnal pain or pain of anginous nature.

Complications.

The disease may be complicated by: (1) Spasm at the site of the cardia with secondary dilatation, and (2) peptic ulcer of the oesophagus.

(1) Spasms are encountered especially in nervous and neuro-

pathic children. They are often intermittent, and this is probably the explanation of the periodical occurrence of the vomitings. In other cases, if the spasm is permanent, it may cause dilatation of the proximal portion of the oesophagus, causing stagnation of food particles and the development of oesophagitis. In turn, the oesophagitis may produce a spasm, and a vicious circle has been created.

(2) In connexion with the oesophagitis the spasm may form a favourable condition for the formation of a peptic ulcer of the oesophagus. At the present time, it is, however, impossible to say how frequently brachyoesophagus is attended with ulcer, but the latter may be encountered at all ages, most often between 40—50. (Among children aged 8 months to 15 years DORN has observed 9 cases of peptic oesophageal ulcer.)

Like the main disease the complicating ulcer may run a symptomless course in exceptional cases, but usually it calls attention to itself by severe pain either in the upper part of the epigastric region or behind the lower part of the sternum, sometimes to the left of the latter radiating along the costal borders or to the shoulder blades. The pain may set in as soon as the food is swallowed or later, 1/2-1 hour after meals. Dysphagia, regurgitation and vomiting are symptoms common for brachyoesophagus and peptic ulcer of the oesophagus, whereas hæmatemesis and melæna are practically certain signs of a complicating ulcer. In rare cases a fatal perforation is the first sign of the presence of an ulcer. (A more detailed description of the clinical features of peptic ulcer of the oesophagus falls without the scope of this paper. Reference should be made to more elaborate surveys published by FRIEDENWALD, FELDMANN & ZINN, RÖJDEMARK, and HINDSE-NIELSEN.)

Diagnosis and Differential Diagnosis.

It is difficult to make the diagnosis and hardly at all possible without an X-ray examination. Numerous cases have, no doubt, been overlooked, others have been interpreted as pure oesophageal spasms or erroneously diagnosed as diaphragmatic hernia on the

basis of an X-ray examination. Lastly, a number of cases have not been diagnosed until the post-mortem examination. During infancy the syndrome is by no means characteristic, but in small children, older children, and adults the dysphagia in conjunction with pain and vomiting will quickly lead one to suspect an oesophageal disorder.

In infants the differential diagnoses consist of hyper- or hypogalactia, congenital pyloric stenosis, atresia, or stenosis of the oesophagus, more rarely duodenal stenosis. In older children and adults the syndrome with as well as without hæmorrhages may be mistaken for gastric disorders. - Therefore X-ray examination is an absolute necessity in most cases of vomitings of uncertain etiology. During childhood this diagnostic procedure is extremely difficult, and usually a special technique is required for a successful demonstration of brachyoesophagus with a partial thoracic stomach. The patient must be examined standing (perhaps sitting), in the right oblique position, in the horizontal position, and finally in the Trendelenburg position, if possible also during deep inspirations. While the patient is being examined with the fluorescent screen he must be turned from side to side, and when he is in the recumbent position, one must be sure that the fundus ventriculi is properly filled. In case the examination fails to give a result, it should be repeated some time after.

In order to make an X-ray diagnosis one must demand: (1) that part of the stomach is above the diaphragm, and (2) that the oesophagus apparently is so short that it does not reach as low as the level of the diaphragm.

- (1) The characteristic sign of this condition is the presence of multiple longitudinal folds of mucosa in the part of the alimentary canal running through and above the diaphragm. In addition, changes in the patient's position must not influence the situation of the supra-diaphragmatic part of the stomach.
- (2) The oesophagus must be examined in its entire length at different angles and positions in order to rule out a tortuous course, and it must be proved that the narrow part is unable to reach as low as the diaphragm.

Moreover, an X-ray examination will usually reveal a broad

communication between the thoracic and abdominal stomach corresponding to a hiatus oesophageus of abnormally large dimensions.

Oesophagoscopy is a factor of considerable value in diagnosing this anomaly. In this country it is, however, a very rare diagnostic procedure, so the writer will restrict himself to a brief mention of the oesophagoscopic picture. The findings are said to be:

- Dilatation of the upper portion of the oesophagus attended with chronic oesophagitis.
- (2) Circular or tunnel-shaped stenosis on a level with the 7th thoracic vertebra, and in some cases, oral to the stenosis, a superficial ulceration covered with a greyish substance.
- (3) Gastric mucosa below the stenosis.

Treatment.

The treatment is symptomatic. Bouginage of the stenosis is dangerous and in most cases ineffective. Operative treatment is seldom indicated.

During infancy one may advise small, frequent meals, perhaps taken in the erect position, and in the case of older children one must as far as possible administer a diet of fluids.

During the bad spells which, as mentioned above, are presumably due to spasms, the thing to do is to treat the causative oesophagitis. In our department we have, as far as possible, given these children a fluid diet, and moreover, we have made them drink large amounts of water after meals (in order to rinse the oesophagus of food particles). In a few cases we have administered phenemal with a good effect.

Summary.

The writer reports 4 cases of brachyoesophagus and briefly mentions the theories advanced regarding its etiology as well as the histological findings.

Vomiting is the main symptom. It may appear immediately after birth or in the course of the first weeks of life, though some-

times not until solid food is taken. A characteristic symptom is daily vomiting occurring during meals. The vomitus is alimentary, slimy, rarely bloody, and the food is returned without effort. Frequently the course is periodical.

Complications are: (1) Spasm at the site of the cardia with secondary dilatation, and (2) peptic ulcer of the oesophagus.

Stress is laid upon the necessity of performing an X-ray examination, and the technique of the latter is described.

The treatment consists in frequent, small meals of a fluid diet, supplemented with administration of phenemal. In addition, older children should be given large quantities of water after meals in order to prevent oesophagitis.

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Maladies chez enfants de réfugiés polonais en Allemagne.

Par

OLAF NORGAARD, Copenhague.

Pendant l'hiver 1945—46 où j'étais médecin auprès de l'U. N. R. A. en Allemagne, j'avais beaucoup d'occasions pour étudier les traces qu'avaient laissées la famine et les misères de la guerre chez les Polonais, surtout chez la jeune génération. J'ai alors commencé à examiner systématiquement tous les enfants dans les camps sous ma surveillance, et j'ai tenu un journal pour chaque enfant. En décembre 1945 et en janvier 1946, où je me trouvais à Mölln, j'ai examiné 127 enfants sur cette place. Malheureusement le travail ne fut pas achevé, parce que j'ai été transféré à un autre camp. En février et mars 1946, où j'étais à Rendsburg, j'ai examiné 120 enfants dans cette ville, et c'est le résultat de cet examen que je vais présenter ici.

Les parents de ces enfants avaient pour la plus grande partie été en Allemagne pendant 5—6 ans; les allemands les avaient conduits dans leur pays pour les faire travailler dans les usines et l'agriculture. Quelques-uns n'étaient arrivés en Allemagne que six mois avant la fin des hostilités; ils avaient fuit devant les Russes pendant leur dernière offensive en Pologne. Tant les hommes que les femmes avaient eu du travail dur, les femmes parfois jusqu'à quelques jours avant l'accouchement. Les accouchements eurent souvent lieu à la maison, mais pour environ la moitié des cas faisant l'objet de l'examen, dans une clinique ou à l'hôpital. Comme la mère devait ordinairement travailler de nouveau peu de temps après l'accouchement, elle n'avait que rarement l'occasion d'allaiter l'enfant au sein. En conséquence, la plupart des

enfants nés pendant la guerre n'avaient été allaités au sein que pendant une période très courte. Cela forme un contraste absolu à l'usage des Polonais en temps normal, où les mères donnent souvent le sein aux enfants jusqu'à ce qu'ils soient âgés de deux ans. En ce qui concerne la nourriture, il y avait de grandes diversités. Voici les rations officielles pour les ouvriers polonais en Allemagne en 1942. Rations hebdomadaires: 1600 g de pain noir, 1 100 g de pain de seigle bluté, 125 g de beurre, 80 g de margarine, 300 g de viande, 60 g de fromage et 150 de "Nährmittel". En outre on donnait 1/2 litre de lait complet par jour aux femmes enceintes et allaitantes, et les enfants recevaient aussi du lait complet. En faisant des interrogations on constata que ces rations ne furent pas toujours observées, mais d'un autre côté il y avait beaucoup d'endroits à la campagne où les ouvriers polonais avaient leurs repas avec les paysans et où ils recevaient plus que fixé par les rations officielles.

Immédiatement après la capitulation le 5 mai 1945, les armées anglaise et américaine ont pris en charge l'entretien des réfugiés. Plus tard l'U. N. R. R. A. s'est chargée de leur ravitaillement, et les réfugiés furent assemblés dans des camps partout où cela était possible. A Mölln les réfugiés habitaient dans des maisons réquisitionnées des Allemands, à Rendsburg ils étaient logés dans des camps composés de baraques de bois.

En examinant les enfants à Rendsburg j'ai demandé dans chaque cas spécial si l'enfant en question avait des frères et sœurs qui étaient morts pendant la guerre. Il a été mentionné au total 20 enfants, frères et sœurs des enfants examinés, qui étaient morts pendant cette période. Cinque étaient morts quelques jours après la naissance, quatre étaient morts de pneumonie, mais d'une façon générale les mères ne pouvaient donner que des renseignements rares et peu précis sur la cause du décès, de même que par cette méthode on n'est pas informé de tous les enfants qui sont morts. On a des soupçons que le nombre réel est beaucoup plus élevé que les 20 enfants mentionnés, en regardant la table ci-après qui indique la classification par âge des enfants à Mölln, Büdelsdorf et Jägerslust:

Mois:	0	1	2	3	4	5	6	7	8	9	10	11	7	Total
Jägerslust	9	3	4	2	2	4	2	1	1	0	1	1	30	enfants
Büdelsdorf	1	2	4	5	3	1	0	2	0	2	2	0	22	3)
Mölln	5	4	2	2	3	6	3	3	5	0	0	2	35	19

La classification par âge pour les enfants de plus d'un an résulte de la table suivante:

Ans:	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Jägerslust	15	12	4	3	6	2	4	7	10	4	5	7	4	6
Büdelsdorf	10	14	14	18	7	3	8	3	4	5	2	11	5	7
Mölln	12	5	9	11	6	3	5	6	3	5	10	6	7	4
Total	27	91	97	90	10		17	1.0	17	1.4	17	9.4	14	17

Dans les trois camps il y avait au total 87 enfants âgés de moins d'un an, c. à. d. plus de deux fois le nombre d'enfants des générations ayant survécu à la guerre. Comme il n'y a pas lieu de supposer que la natalité a tellement augmenté pendant la dernière année, cela témoigne d'une très grande mortalité d'enfants pendant la guerre. On peut aussi l'expliquer par le fait que beaucoup de grossesses, qui se seraient peut-être terminées par avortement, ont été menées à terme, maintenant que les mères pouvaient vivre dans des conditions plus tranquilles.

La table de Jägerslust arrêtée au 1^{er} avril montre en outre une augmentation violente des naissances commençant vers le 1^{er} mars. Malheureusement je n'ai pas eu l'occasion de poursuivre les examens, mais à en juger par le nombre de femmes enceintes, cette « conjoncture de capitulation » — l'effort de la nature de réparer les pertes subies par la nation polonaise pendant la guerre — augmentera ultérieurement au cours des mois suivants. On ne trouve pas cette augmentation du nombre de naissances dans les tables pour Büdelsdorf et Mölln, celles-ci étant arrêtées le 1^{er} mars et le 1^{er} février respectivement.

L'U. N. R. A. à Rendsburg a pourvu aux besoins d'env. 2 200 réfugiés polonais logés dans les camps de Büdelsdorf, Jägerslust, Hohn et Blumenthal. Les enfants examinés sont tous de Büdelsdorf. Ce camp a été choisi parce qu'il était situé le plus près de Rendsburg, et il y avait env. 1 000 réfugiés. Ordinaire-

ment on a examiné 15 enfants par jour. Les enfants sont venus dans le local d'examen accompagnés de leurs mères. Environ un tiers des mères pouvaient parler allemand; on devait questionner d'autres par l'intermédiaire d'un interprète. Les renseignements que pouvaient donner les mères concernant les maladies antérieures, la durée de la période d'allaitement au sein, la sortie de la première dent, etc., étaient très insuffisants et paraissaient être peu précis. Cependant cela était dû non seulement à une mauvaise mémoire mais aussi au fait que beaucoup d'entre elles avaient été séparées de leurs enfants pendant de longues périodes. Après la constatation des signes anamnestiques, l'enfant a été examiné par stéthoscopie, inspection du pharynx, etc. Puis l'enfant a été mesuré et pesé par l'infirmière, et les dents ont été examinées par un dentiste polonais et le résultat noté dans le journal.

En ce qui concerne le nombre d'enfants, tous les matériaux comprenaient 15 familles avec 2 enfants, 8 avec 3, 8 avec 4, 2 avec 5, 1 avec 6 et 3 familles avec 7 enfants. Il n'y avait que deux orphelins. Leur mère était morte en 1943 de tuberculose, et le père avait — selon ce qui était indiqué — été forcé à s'enroler dans la « Wehrmacht », et l'on n'avait pas de renseignements sur lui. Ce n'était pas possible de constater combien des enfants avaient été nés hors du mariage, car les réfugiés n'avaient que rarement des papiers, et il s'est trouvé qu'on ne pouvait pas se fier à leurs renseignements à ce sujet.

Concernant le poids des enfants à la naissance, j'ai reçu des mères des renseignements tellement fantastiques et imprécis que j'ai bientôt renoncé à les questionner à ce sujet. Au lieu de cela, j'ai indiqué ci-dessous le poids de naissance d'enfants polonais nés dans la « Universitätsfrauenklinik » à Kiel. Le chiffre entre parenthèse signifie le nombre de naissances dans le mois en question.

Mai Juin Août Décembre 1945 Janvier 1946 3 020 g (5) 3 709 g (6) 3 310 g (8) 3 620 g (13) 3 605 g (7)

Chez deux enfants, à savoir journal no. 8 et no. 15, il y avait un grave craniotabes. Ils étaient tous les deux nes avant terme, étaient tous les deux nourris au biberon et n'avaient jamais reçu de

²⁰⁻⁴⁷³⁴⁰ Acta Padiatrica. Vol. XXXIV

l'huile de foie de morue à cause de l'animosité des mères contre médicaments. Le plus jeune, qui avait 3 mois, ne pesait que 3,7 kilos (poids normal 5,5 kilos). L'autre, qui avait 4 mois, pesait 5 kilos (poids normal 5,5 kilos). A part ces deux enfants, il n'y avait pas de cas de rachitisme actuel; on ne devait pas non plus s'y attendre, car depuis décembre 1945 tous les enfants avaient régulièrement reçu de l'huile de foie de morue. Au contraire, il y avait au total 23 enfants présentant des signes de rachitisme antérieur, creux de Harrison, caput quadratum, palatum ogivalum, circulaire défectuosité de l'émail des incisives ou incisives dentelées; surtout les défectuosités des dents étaient fréquentes, cependant le diagnostic n'a jamais été établi sur ce symptôme seul. Chez journ. no. 7, un enfant du sexe féminin âgé de 2 mois, poids 4,1 kilos (poids normal 4,8 kilos) on a constaté une dyspepsie chronique. Cette enfant n'avait été allaitée au sein que pendant un mois, puis la mère lui avait donné du lait non étendu et du poudre de lait. L'enfant a été admise à une maison de santé et est morte un mois plus tard d'une pneumonie survenante. Journ. no. 46, enfant du sexe masculin de 2 ans, né deux mois avant terme. La mère avait travaillé dans une usine pendant la grossesse et avait dû travailler jusqu'au dernier jour avant l'accouchement. L'enfant avait été allaité au sein pendant les premiers 5 mois, plus tard la mère avait reçu 1/2 litre de lait complet par jour pour lui. Il pesait 9,4 kilos (poids normal 12 kilos) mais à l'exception de signes de rachitisme antérieur il n'y avait pas de symptômes de maladies. Journ. no. 80, enfant du sexe masculin âgé de 8 ans, était jumeau. Le frère jumeau était mort à l'âge de deux ans et demi d'une pneumonie. C'était un enfant pâle et maigre, la hauteur était un peu plus grande que la normale, mais le poids était normal. Il avait de grandes tonsilles, une voix nasillarde et sténose nasale, la voûte du palais en ogive et position des dents irrégulière mais pas de carie. Il y avait un abcès à la racine de dent qu'on a incisée. Journ. no. 122, enfant du sexe masculin de 14 ans, poids 36,5 kilos, hauteur 153 cm (poids normal 43 kilos), avait également une hypertrophie des tonsilles, mais abstraction faite du poids insuffisant il n'y avait pas de signes de maladies. En dehors des deux enfants déjà mentionnés, il y avait dans tous

les matériaux deux enfants avec hypertrophie des tonsilles. En outre il y avait 3 enfants avec pityriasis simplex capitis, 1 avec scabies, 1 avec pediculosis capitis, 1 avec impetigo, 1 avec ichtyosis vulgaris, 4 avec hernia umbilicalis, 1 avec pes planus duplex, 1 avec morbilli et 2 avec bronchopneumonie, 2 avec otitis media purulenta et 1 avec rhinite et bronchite. A part les enfants susdits de poids insuffisant, tous les autres enfants avaient le poids normal, il y avait même beaucoup d'entre eux qui avaient du surpoids. (Le poids normal a été basé sur les tables de Monrad, parce que je n'avais pas des tables pour le poids normal chez enfants polonais.)

Chez un des enfants, journ. no. 85, une fille de 8 ans, il y avait 12 cicatrices en forme de bande et env. 1,5 cm de longueur, placés sur le dos en deux rangs et en groupes de deux. Un médecin polonais les avait fait une fois lorsque, toute petite, elle avait une maladie fébrile, pour «faire sortir le mauvais sang» (l'application de ventouses était encore beaucoup en usage chez les Polonais, surtout dans tous les cas de maladies fébriles. Cette opération fut presque toujours faite par la sagefemme, et l'appareillage consistait en 6 écuelles en verre rondes, presque hémisphériques, dont le diamètre était env. 5 cm. On y versait un peu d'alcool qui était enflammé, et puis on les plaçait ordinairement sur le dos ou la partie devant du thorax. Par la dépression ainsi produite, le sang était aspiré par la peau dans l'écuelle).

Ce ne fut qu'un des enfants, à savoir journ. no. 103, une fille de 11 ans dont on avait abusé pour faire du travail dur. La mère était morte en 1945, le père travaillait dans une usine, et ici elle devait travailler dur dans la cuisine de 7 heures du matin jusqu'à 6 heures du soir.

'Un trait qu'on a trouvé chez la plupart des enfants tant à Rendsburg qu'à Mölln est le teint gris pâle et maladif. Chez 10 des enfants à Mölln j'ai déterminé le taux de l'hémoglobine selon la méthode de Sahli, et j'ai trouvé des valeurs de 80—85 % (étalon de Haldane). J'ai aussi déterminé le taux de l'hémoglobine chez une partie des enfants à Rendsburg qui avaient été à l'hôpital ou chez un spécialiste, et j'ai trouvé des valeurs analogues. Un autre trait qui s'est retrouvé chez beaucoup des enfants, sur-

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tout les plus grands, était un grand abdomen ce qui fait penser à des affections digestives antérieures. Ce symptôme ne semblait pas gêner les enfants, et selon les renseignements reçus, les matières fécales étaient d'un aspect normal et la défécation avait lieu journellement.

Comme il y avait beaucoup d'adultes dans les camps — surtout parmi les anciens prisonniers des camps de concentration — qui étaient atteints de tuberculose, j'ai fait examiner au moyen de radioscopie tous les enfants qui étaient assez grands pour pouvoir se placer devant l'écran. Chez 6 de ces enfants, on a constaté un grossissement de hilus, chez 7 il y avait complexe primaire scléreux. Chez 30 parmi les enfants à Mölln qui ont également été examinés de cette manière, il y avait chez 4 d'entre eux complexe primaire scléreux. Il n'y avait pas l'occasion de faire des examens ultérieurs, tels que sédimentation et Mantoux.

Abstraction faite du petit nombre d'enfants malades mentionné ci-haut, les enfants étaient tous d'une bonne santé, et si l'on pense à toutes les souffrances physiques et psychiques qu'ils ont endurées pendant presque 6 années de guerre, on doit admettre qu'ils faisaient une bonne impression. Pendant les 6 mois qui se sont écoulés depuis la fin des hostilités et qu'ils ont passés dans des conditions tranquilles et avec une bonne nourriture, ils semblent avoir complètement oublié toutes les souffrances. Ils ont aussi fait des progrès à l'école. Les enfants au-dessous de 12 ans ont ici, pour la première fois dans leur vie, reçu de l'enseignement. Quelquesuns, qui avaient grandi parmi les Allemands, avaient tout à fait oublié leur langue maternelle et ne parlaient que allemand.

Comme je vient de mentionner, chaque enfant a été examiné en vue de constater des cas de carie. L'examen a été fait du dentiste polonais W. Kubarcz. Chez 87 enfants de plus de deux ans on a trouvé au total 16 dents de lait cariées et 52 dents permanentes avec carie. 57 enfants, c. à. d. deux tiers, étaient tout à fait exempts de carie. Lorsque je me suis rendu compte de ce fait, j'ai examiné, en commun avec la dentiste polonaise Franciska Czelinska, les enfants dans le camp polonais de Jägerslust. Chez 66 enfants de l'âge de 4 à 16 ans nous avons trouvé au total 33 dents de lait cariées et 63 dents permanentes avec carie. 40 en-

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fants étaient complètement exempts de carie. En examinant les enfants à Mölln j'ai noté moi-même combien avaient la carie. Il y en avait 40 sur 83 enfants de plus de deux ans, et alors il y a certainement quelques cas de carie légère qui ont échappé à mon attention.

A titre de comparaison, il convient de citer quelques chiffres des examens de carie dans ce pays et à l'étranger. Hartvig Andersen et Grethe Yde ont examiné 1 268 enfants de l'école municipale à Roskilde (Danemark) âgés de 7—13 ans. Parmi ceux-ci, seulement deux étaient exempts de carie. Gythfeldt indique que sur 25 000 écoliers à Oslo il n'y a que 1,5 % qui sont exempts de carie. Mathis indique que sur 19 725 écoliers dans l'Allemagne du Nord, seulement 5 % sont exempts de carie.

Si l'on demande alors quelle est la cause de cette fréquence de carie exceptionnellement petite, il est très naturel de la chercher dans la nourriture. C'est frappant que celle-ci ne contient pas de sucre. En effet le sucre est un des aliments qui a le plus souvent été supposé de provoquer la carie puisqu'il a une grande valeur calorique et, de ce fait, il empêche la fixation d'autres substances alimentaires protectrices; d'ailleurs le sucre n'a lui-même aucune valeur comme substance protectrice. En faisant des examens dans l'agglomération isolée, Valli, à Setesdal en Norvège, Toverud a démontré que les familles ayant la plus grande consommation de sucre avaient aussi une mauvaise denture. Collett à Oslo a démontré une grande diminution de la fréquence de la carie chez les écoliers pendant la guerre, ce qu'il attribue à la consommation de sucre réduite pendant cette période.

Si cette théorie est correcte, on devrait de nouveau pouvoir constater la carie chez ces enfants au moment où ils reçoivent de nouveau une nourriture contenant la quantité « normale » de sucre. En effet, cela a déjà eu lieu, car les rations délivrées par l'U. N. R. R. A. contenaient 1 kilo de sucre par mois. Cependant, ils n'avaient reçu cette nourriture que pendant 3—4 mois, quand ces examens ont eu lieu.

Résumé.

Pendant l'hiver 1945—46 l'auteur a examiné 311 enfants de réfugiés polonais logés dans les camps de Mölln, de Jägerslust et de Büdelsdorf. L'observation la plus intéressante chez ces enfants était leur basse fréquence de carie.

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Familial Haemorrhagic Diatheses with Prolonged Bleeding-Time (Thrombopathias).

By

OLGA IMERSLUND.

Several hereditary diseases have gradually been sorted out from the variegated collection represented by the haemorrhagic diatheses. During the last decades reports have been published of the familial occurrence of cases which, from the clinical point of view, have been reminiscent of essential thrombopenia, but in which a reduction in the number of thrombocytes has seldom been demonstrable. These cases have represented both sexes. Glanzmann, v. Willebrand, Jürgens and Naegell have described various types which, in their opinion, are inherited as a dominant factor. They have been termed thrombopathias as they are supposed to be associated with a defective function of the thrombocytes. The coagulation-time is normal in these haemorrhagic diatheses whose manifestations vary according to the different types to which they belong.

In GLANZMANN's thrombasthenia, the bleeding-time is, according to his own description which is already a classic, normal when the number of thrombocytes is normal. The characteristic features of this condition are the much reduced or suppressed clotretraction and the abnormal appearance of the thrombocytes which are small, of various sizes, to some extent basophil and without granules. The capillary resistance-test is markedly positive.

The essential feature of constitutional thrombopathia of the Willebrand—Jürgens type is the prolonged bleeding-time and, in severe cases, a positive capillary-resistance test.

The bleeding-time is prolonged also in the NAEGELI type. The morphology of the thrombocytes resembles that found in GLANZ-MANN'S thrombasthenia. Clot-retraction is markedly reduced, and the capillary-resistance test is markedly positive.

In the JÜRGENS type, the bleeding-time, clot-retraction, and the appearance of the thrombocytes are all normal. The capillaryresistance test is markedly positive.

Only among GLANZMANN's cases and others resembling them (KRÖMEKE, DILTHEY) have accounts been given of severe degrees of thrombopenia.

The cases to be discused here belong to three families in different parts of the South of Norway. The pedigrees are in part compiled on the basis of personal communications from members of these families still alive, in part on the basis of church books and national census lists.

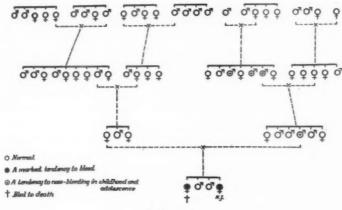
Family 1. Pedigree 1.

A girl, K. I., born 13.12. 1943, was treated in the Children's Department of the Rikshospital between 15.2. 1946 and 25.2. 1946. The youngest of four. Normal birth and weight at birth. Nothing remarkable about her feeding. Physical and mental development normal. Since the age of 6 months apt to suffer from nose-bleeding and to bruise when knocked. The nose-bleeding seemed to arise without any provocation, for example when she slept, and it was not worse when she had a cold. Repeatedly admitted to Drammen Hospital for bleeding from cuts and for nose-bleeding. Plugging the nose with tampons often necessary, and the bleeding gave rise to signs of acute anaemia.

From records in the Drammen Hospital: Tibia puncture 19.3. 1945: smear rich in cells. Normoblastosis. Number of lymphocytes increased. Nothing noteworthy with regard to myelopoiesis or the reticulum cells. 21.3. 1945, Hb. 90%, erythrocytes 4.99 millions, thrombocytes 188 000, bleeding-time 26 min., coagulation-time 5—6 min. 31.3. 1945, thrombocytes 179 000. Nose-bleeding at this date. A few petechiae observed in Drammen Hospital.

In December 1945, when fully 2 years old, and before her





Pedigree 1.

admission to the Children's Department of the Rikshospital, she developed gas phlegmon in the leg below the knee on the right side and osteomyelitis of the right tibia starting from a needle puncture entailed by a blood transfusion. For the time being blood transfusions were discontinued because it was impossible to find a suitable vein. Later on she also developed an acute otitis. While in the Children's Department she was rather pale and presented a few irregular, blue and bluish-green patches up to the size of a penny in her skin at various places. No petechiae. An ordinary clinical examination showed nothing else noteworthy. Lymphatic glands, liver and spleen showed no enlargement. Blood pressure 60 mm (systolic). Afebrile. Urine: no albumin, no sugar, no blood. Nil on microscopic examination. S. R. 20 mm (micro). Hb. 52 %, erythrocytes 3.13 mill., leucocytes 8 400. Differential count: eosinophils 1.5 %, neutrophils, band forms 4.5 %, polymorphs. 32 %, lymphocytes 54.5 %, monocytes 7.5 %, reticulocytes 32 %. In a blood smear the erythrocytes showed microcytosis with slight anisocytosis and poikilocytosis. Slight polychromasia. At two examinations a few days apart the number of thrombocytes (Fonio) was 445 000 and 380 000 respectively. Simultaneously the bleeding-time (Duke) was 1 hour and 2 hours respectively. The coagulation-time (Wright's method with capillary tubes) was 3 min. and 2 min. Prothrombin-time normal. Satisfactory clot-retraction on both occasions (50 % retraction after 1 hour in thermostat at 37° according to Macfarlane's method). Leede Rumpel negative, the JÜRGENS pinching test positive. The knocking test positive. Koch's pin-prick test positive. Serum Calcium 11 mg %. Serum proteins 6.28 %, of which albumin 4.63 %, globulin 1.65 %. Fibrinogen 0.25 %. Non-protein nitrogen 34 mg %. Blood Wassermann negative. Mantoux $^{1}/_{10}$ mg negative. Roentgenological examination of chest, skull, wrists negative. Fundus oculi normal. An examination of the ear, nose and throat showed no signs of telangiectases or other abnormalities.

A blood smear was sent to Professor v. WILLEBRAND, Helsingfors, eliciting the following report on the thrombocytes:

"Thrombocytes are quite numerous in the smear preparation, for the most part scattered, but also clustered in large or small groups. The thrombocytes show greater variations than in the previous case (i. e. S. B. who was the first to be examined). With regard to size, microthrombocytes are to be seen but are not too numerous. There is also a smaller quantity of macrothrombocytes of various shapes, round, cylindrical, and basket-shaped. No giant thrombocytes. Azure-granulation is well developed, and the protoplasm is on the whole light. In some thrombocytes the granules are coarser and darker in colour, and in some of the latter the granules are collected in the periphery, showing a tendency to granulapyknosis. The macrothrombocytes, particularly the cylindrical and basket-shaped, are a kind of normal reactive form, and need not necessarily be pathognomonic of thrombopathias. In brief, it may be said that the patient in question presents no markedly pathological forms of thrombocytes."

This patient's sister, the eldest of the family, died of nosebleeding when 1 ½ years old. A month before the fatal haemorrhage she bled from her gums and presented a few blue patches in her skin. Two brothers, nrs. 2 and 3 in the family, are healthy, as are the parents who are not related to each other. The father, the paternal grandfather, and two of his brothers were liable to suffer from nose-bleeding. Neither the father nor the paternal grandfather bruised very readily, nor did they bleed for long from wounds. No information concerning a tendency to bleed in other members of the family.

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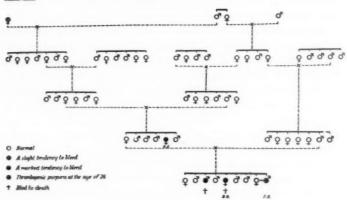
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Nothing noteworthy about the examination of the mother (born in 1911) and the father (born in 1913) nor in the patient's two brothers and paternal grandfather (ordinary clinical examination, Hb. percentage, erythrocyte and leucocyte counts with differential counting, thrombocyte counting, and examination of the bleeding-time, coagulation-time, and clot-retraction).

Family 2. Pedigree 2.

A girl, B. B., born 9.8. 1938, was admitted to the Children's Department of the Rikshospital 9.6. 1942, being discharged 26.6. 1942. She is nr. 5 in the family. Normal birth and weight at birth. Nothing remarkable about her feeding. Since 10 weeks old, she has constantly presented small red patches in the skin and has been subject to nose-bleeding and prolonged bleeding from wounds. No swelling of joints observed. On admission to hospital she presented numerous ecchymoses on trunk and limbs and some blue and yellowish-green, slightly infiltrated patches ranging up to the size of a 5-öre piece. The petechiae and ecchymoses disappeared during her sojourn in hospital, but she bruised readily when knocked. Otherwise nothing noteworthy on an ordinary clinical examination. Her appearance was healthy, and she was afebrile. No enlargement of the lymphatic glands, liver or spleen. Urine light yellow, clear, no albumin, no sugar, no blood, Schlesinger negative. Ascorbic acid in serum 0.32 mg %. S. R. 9 mm (micro). Hb. 90 %. Erythrocytes 4.9 mill., leucocytes Differential count: eosinophils 7%, neutrophil band forms 1 %, polymorphs. 20 %, lymphocytes 67 %, monocytes 5%. Coagulation-time 3 min. Bleeding-time 15 min. At the same time the thrombocytes numbered 185 000. At two later examinations they numbered 104 000 and 190 000. Leede Rumpel negative. Blood Wassermann negative. Mantoux 1/10 mg negative. She was to have returned to the hospital for re-examination that autumn, but she did not appear. In May, 1943, a severe haemorrhage from a sore in her mouth. Admitted the same day to Not-





Pedigree 2.

odden Hospital, but she died a few hours after admission with signs of acute anaemia.

Her brother, S. B., born 10.4. 1945, was treated in the Children's Department of the Rikshospital on the first occasion between 31.10. 1945 and 17 12. 1945 and on the second occasion between 4.9. 1946 and 6.9. 1946. He is the youngest of 8. Normal birth and weight at birth. Nothing remarkable about his feeding. Breast-fed till he was half-a-year old with supplementary feeding after the first few weeks. Since the age of 6 months a supplement of vegetables and fruit, and since the age of 9 months an ordinary mixed diet. Since he was only a few days old he was constantly subject to the development of red and blue patches in his skin. Occasionally, and when he had caught a cold, he suffered a little from nose-bleeding. On occasions he has bled for several hours after being stung by a fly. No swelling of his joints observed. During his first stay in hospital he constantly developed bruises, particularly in his face which he knocked against a glass wall. After puncture of a vein in his neck, several petechiae appeared in his face. Few petechiae elsewhere. Otherwise nothing noteworthy on an ordinary clinical examination. No enlargement of the lymphatic glands, liver or spleen. Blood pressure 70/50.

Urine: no albumin, no sugar, no blood. Nil on microscopic examination. At a few examinations slight anaemia, hypochromic or normochromic, was observed. As a rule, the haemoglobin ranged between 67 and 76 %. Erythrocytes between 3.6 and 4.65 millions. In a blood smear the erythrocytes showed slight anisocytosis and polychromasia.

During the first weeks in hospital he had a cold and presented slight leucocytosis with shift to the left, the leucocytes showing no definite departure from the normal in other respects. On admission to hospital the thrombocytes numbered 42 000. Nine days later they numbered 287 000. Frequent examinations subsequently showed figures ranging from 249 000 to 548 000, all the counts being made according to Fonio's method. At the same time as the thrombocyte counts, repeated examinations were made of the bleeding-time, the coagulation-time, the clot-retraction and the prothrombin-time. The bleeding-time (Duke) varied between 13 min. and 3-4 hours. The coagulation-time (Wright's method with capillary tubes) varied between 2 and 5 min. At the same time that the number of thrombocytes was normal, the clot-retraction was 40-42 % (Macfarlane). The appearance and consistency of the clot and the prothrombin-time were normal. Leede Rumpel was partly negative, partly faintly positive. The JÜRGENS pinching test, and Koch's pin-prick and knocking tests were all definitely positive.

Tibia puncture undertaken on the patient's admission to hospital and at the same time that the thrombocytes numbered 42 000 showed a slight increase of the megakariocytes and lively erythropoiesis, whereas there was nothing noteworthy with regard to the leucopoiesis. In a later specimen there was no definite increase of the megakariocytes, and there was no change in other respects. Calcium in serum 10.4 mg %, ascorbic acid in serum 0.43 mg %. Serum proteins 7.04 %, of which albumin 4,29 %, globulin 2.75 %. Non-protein nitrogen 19.53 %, fibrinogen 0.35 %. Blood Wassermann negative, Mantoux $^{1}/_{10}$ mg negative, no blood in the faeces on several occasions. A Roentgenological examination of the wrists, skull, spine and chest negative. Fundus oculi normal. Professor v. Willebrand's report on the thrombocytes:

"On the whole the thrombocytes are normal with moderate variations in size. No giant thrombocytes found. Protoplasm light. Azure granulation well developed. No granulation-free elements, no granulapyknosis. In fact, no pathological forms. The thrombocytes are evenly distributed in the blood preparation, being at no point agglutinated and clumped together in groups as often seen in blood from healthy persons. This suggests that the agglutination-capacity of the thrombocytes is defective."

After discharge from his first stay in hospital, the patient showed no change in his condition for a long time until the end of the summer 1946 when an increase of the cutaneous haemorrhages coincided with a cold. During his second stay in hospital there were more numerous petechiae and a certain number of ecchymoses. S. R. 14 mm (micro). Hb. 70 %. Erythrocytes 3.97 millions, leucocytes 3 900. Differential count: neutrophil band forms 4 %, polymorphs. 28 %, lymphocytes 60.5 %, monocytes 7.5 %. Bleeding-time 12 min.—\(^1\)_2 hour. Coagulation-time 2 min. Leede Rumpel negative.

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The twin sister of S. B. is healthy. Nr. 3 in the family was a boy who died at the age of $2^{1}/_{2}$ years from haemorrhage from a cut on his lip. The doctor who treated him stated that he had had cutaneous haemorrhages since he was 10 weeks old. The parents are healthy and have never noticed any tendency to bleed excessively. They are related to each other. A maternal aunt, G. S., had cutaneous haemorrhages and nose-bleedings when 26 years old. A great-great-grandmother of the children bled readily and developed blue spots in her skin on slight provocation. An examination of the father, O. B., (born in 1892) of the mother, (born in 1906) and of their 5 other children showed nothing of special interest, the examinations being the same as those carried out on the relations of the patient in the first family.

The maternal aunt, G. S. (born 28.11. 1916) was admitted to the St. Joseph's Hospital, Porsgrunn, 18.12. 1942. From records in this hospital: She has hitherto always been well, and has never shown a tendency to bleed excessively. Five weeks before admission to hospital she developed slight jaundice, with dark urine and pale motions, after she had suffered for some days from nausea and vomiting. Her jaundice coincided with bleeding from

gums and nose. Cutaneous haemorrhages later on. No pain. No drug had been taken before or after she fell ill. She had lived on the usual diet of a mountain farm. On her admission to hospital, blood was oozing from nose and gums, and she presented numerous petechiae. She was no longer jaundiced. Temp. 40.1°, pulse 112, regular, blood pressure 130/80. No enlargement of the lymphatic glands. Liver palpable 1 finger-breadth below the costal arch. Spleen not palpable. Nothing noteworthy on an ordinary clinical examination.

The following examinations were carried out: Urine acid, sp. gr. 1030, no albumin, no sugar, no blood, Gmelin, Hay, Ehrlich, all negative. S. R. 123 mm. Hb. 84 %. Leucocytes 10 500. Thrombocytes 10 000. Coagulation-time 3 1/2 min. Bleedingtime over 10 min. Prothrombin-time normal. Leede Rumpel markedly positive. MKR. II negative. Sternal puncture yielded a specimen rich in cells and with lively erythropoiesis and leucopoiesis. Megakariocytes seemed to be present in normal quantities. The temperature fell by lysis, and by 21.12. 1942 it had fallen to 38.5°. On the day after admission to hospital she was given a transfusion of 500 cc. of citrated blood. As her nose-bleeding continued, splenectomy was performed at the Lutheran Hospital, Porsgrunn, 21.12. 1942. The spleen was but slightly enlarged and soft. By 22.12. 1942, the number of thrombocytes had risen to 125 000, and by 7.1. 1943, the number had risen to 445 000. The bleeding-time was now 3 min., the coagulation-time was 3 min., the Hb. was 81 %, the erythrocytes 4 millions, the leucocytes 10 000, the S. R. 39 mm. Except for a slight febrile reaction immediately after the operation, she was subsequently afebrile.

After the patient's discharge 13.1. 1943, she felt well and has not shown any tendency to bleed excessively. When reexamined in November, 1945, she was in the third month of pregnancy. Nothing else noteworthy, and the liver in particular was not palpable. Hb. 98%, erythrocytes 4.82 millions. Nothing noteworthy about the erythrocytes in a blood smear. Leucocytes 12000. Differential count: eosinophils 2%, neutrophil band forms 13%, polymorphs. 49%, lymphocytes 30%, monocytes 6%. Thrombocytes 207000. Nothing noteworthy about their appearance. Bleeding-

time, coagulation-time, and clot-retraction all normal. Reticulocytes 3 ‰. Icteric index 3 (Meulengracht). The parents of G. S. are related to each other, but neither they nor any of her 5 brothers and sisters have shown any tendency to bleed excessively.

Family 3. Pedigree 3.

A boy, K. H., born 2.7. 1941, was treated in the Children's Department of the Rikshospital on the first occasion between 24.8. 1945 and 4.9. 1945 and on the second occasion between 27.9. 1946 and 13.10. 1946. He is the oldest in the family. Normal birth and weight at birth. Nothing remarkable about his feeding. Since the age of 1 year he has shown a tendency to develop blue patches in his skin partly as a result of knocks, partly, it would seem, spontaneously. On occasions he has bled for 6 to 7 hours from a wound, and he has sometimes suffered from nose-bleeding. Swelling of his joints never observed. In hospital many bruises were observed, notably on the legs below the knees, and also a few petechiae. Nothing noteworthy on an ordinary clinical examination. No enlargement of lymphatic glands, liver or spleen. Blood pressure 100/60. Urine: no albumin, no blood, no sugar. Nil on a microscopic examination. At some of the examinations a slight hypochromic or normochromic anaemia was found, but there was otherwise nothing particularly remarkable about the erythrocytes or the leucocytes.

An examination 25.8. 1945 showed Hb. 68%, erythrocytes 4.16 millions, leucocytes 7 000. Differential count: eosinophils 3%, neutrophil polymorphs 48%, lymphocytes 44%, monocytes 5%. Sternal puncture 28.8. 1945 showed lively erythropoiesis. No definite increase in the number of the megakariocytes. Sternal puncture 30.9. 1946 showed lively erythropoiesis and leucopoiesis a slight increase in the number of the megakariocytes. The coagulation-time (Wright's method with capillary tubes) varied between 1 and 3 min. Prothrombin-time normal. The number of thrombocytes, the bleeding-time, and the coagulation-time are indicated in the following table.

Leede Rumpel was partly negative, partly faintly positive. Even when there was well-defined thrombopenia, it was not

Thrombocytes (Fonio's method)			ng-time method)	Clot-retraction after 1 hr. in thermostat at 37° (MACFAR- LANE's method)	Clot-retraction after 24 hr. at room tempera- ture		
1945							
25.8.	8 300	15	min.				
28.8.	10 600						
31.8.	16 000						
1946							
11.5.	230 000	45	»				
(Farsund	Hospital)						
28.9.	300 000	15)×				
30.9.	204 000						
2.10.	187 000	30	39	10 %	23 %		
4.10.	282 000	30	39				
7.10.	153 000	6 1/	3 »				
9.10.	141 000						
11.10.	223 000	7	26	8 %	34 %		
14.10.	208 000	9	»				

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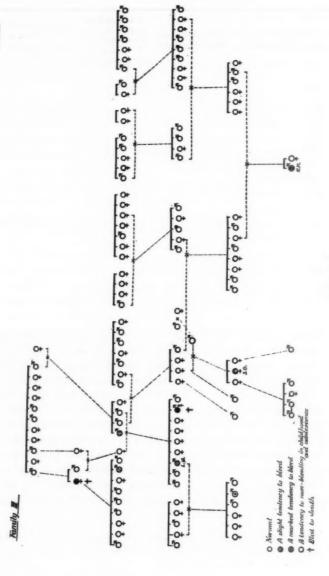
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markedly positive. The JÜRGENS pinching test positive. During the patient's first stay in hospital an examination of ears, nose and throat showed dilated veins on the anterior portion of the septum which were cauterized. During his second stay in hospital he had several attacks of nose-bleeding, but apart from this bleeding nothing abnormal was found in his nose. On 3.10. 1946, serum proteins 7.28 %, of which albumin 3.34 %, globulin 3.94 % A/G 0.24 %. Non-protein nitrogen 19.96 mg %. Fibrinogen 0.31 %. Ascorbic acid in serum 0.42 mg %. Serum calcuim 10.58 mg %. Electrocardiogram normal. Roentgenological examination of the chest normal. Blood Wassermann and Mantoux ($^{1}/_{10}$ mg) negative. Professor v. WILLEBRAND reported on the blood smear sent him:

[&]quot;Thrombocytes are quite numerous, 4 to 5 in some fields of vision. All the elements are scattered, not collected in groups. This seems to 21-47340 Acta Padiatrica. Vol. XXXIV



Pedigree 3.

indicate a defective capacity for agglutination. All the thrombocytes are normal with regard to size and shape. Their diameter would seem to vary between 2 and 4 μ , most being circular and with a well-defined outline. A few are cylindrical or basket-shaped. No giant thrombocytes. Hardly any microthrombocytes. Protoplasm light red, never basophil. Azure granules normal in number, size and position, in a few elements appearing as dust, in others quite coarse and highly coloured. Yet, there is not any marked granulapyknosis. Conclusion: The thrombocytes are normal in size, shape and structure."

The younger sister of K. H. is well. His parents are well and not related to each other. His mother has never noticed any tendency to excessive bleeding. She (born in 1913) and the father (born in 1911) and the sister were examined at the Outpatient Department of Farsund Hospital in October 1946. The mother gave a faintly positive Leede Rumpel test, but otherwise the examination revealed nothing noteworthy. The number of thrombocytes was over 280 000 in all three of them (they were examined in the same way as the relations of the patients already referred to in families 1 and 2).

On the father's side of the family of K. H. no one was found to suffer from a tendency to bleed excessively, but on the mother's side there were several such cases.

The mother's cousin, S. O., (born in 1903) has as far back as she can remember been liable to develop patches in her skin when knocked, and to bleed for a long time when wounded. She has seldom had nose-bleeding. Menses not remarkably profuse. Operated on several times at the Surg. Dept. B. of the Rikshospital for a cyst of the jaw. She has bled much after these operations. Petechiae not observed.

An examination at the Outpatient Dept. of Farsund Hospital in November 1946 showed: Hb. 58 %, erythrocytes 4.33 millions, leucocytes 5 100. Differential count: basophils 1 %, neutrophil band forms 2 %, polymorphs 62 %, lymphocytes 31 %, monocytes 5 %. Thrombocytes 488 000. Bleeding-time over 40 min. Coagulation-time 8 min. Leede Rumpel positive.

S. O. has a half brother and two sisters who are healthy. Her parents are not related to each other, and have shown no signs of a haemorrhagic diathesis. Her mother is alive and well, her father died of old age. A brother of her maternal grandfather, who is also a brother of one of the great-grandparents of K. H. (see the pedigree of family 3) was also liable to bleed excessively, a doctor having repeatedly to be summoned to arrest haemorrhages from wounds and from his nose.

L. Ø. (born in 1873) is a son of a brother of this man. As far back as be can remember he has been liable to develop blue patches in his skin and to bleed for a long time when wounded or after the extraction of a tooth. This tendency to bleed was most marked when he was younger. An examination at the Outpatient Department of Farsund Hospital in November 1946 showed Hb. 99 %, erythrocytes 4.94 millions. Differential count: basophils 1 %, neutrophil band forms 1 %, polymorphs 57 %, lymphocytes 39 %, monocytes 2 %, thrombocytes 254 000. Bleedingtime 20 min., coagulation-time 4 ½ min. Leede Rumpel positive.

L. Ø. is one of a family of 9, and he had a brother who is said to have died in infancy of an intestinal haemorrhage. His other brothers and sisters have not apparently shown any tendency to bleed excessively, nor have his parents (who were related to each other) done so. A sister of the maternal grandfather of L. Ø. is said to have bled readily. She died of a haemorrhage during her confinement. One of her sons was subject to nose-bleeding and to prolonged bleeding from a wound. He was liable to develop blue patches in his skin. His death at the age of 36 was due to renal disease.

The wife of L. Ø. did not bleed excessively. He has had 6 children, the youngest of whom was much troubled by nose-bleeding as a schoolboy. But he has never bled for a long time from a wound, nor has he been liable to develop blue patches in his skin. When he underwent the same examination as that of his father at the outpatient quarters of the Children's Department of the Rikshospital in October 1946, nothing remarkable was found.

Comment.

In each of these three families there are several persons showing signs of a haemorrhagic diathesis. In all the examined cases the bleeding-time was found to be prolonged. Among the cases

in the last two families thrombopenia and diminished clot-retraction were observed at certain of the examinations. The number of thrombocytes was normal, and their morphology presented no important departure from the normal. The coagulation-time and prothrombin-time were normal. Apart from the sequels to haemorrhages and infections, nothing pathological was found in the erythrocytes or leucocytes.

The familial occurrence of these cases is indicative of hereditary haemorrhagic diatheses. Haemophilia can be excluded because the coagulation-time was normal and because the women presented severe manifestations of a haemorrhagic diathesis. Constitutional fibrinopenia (in which a prolongation of both the bleeding-time and coagulation-time occurs) can also be excluded. Besides, the fibrinogen content of the blood, investigated in several of these cases, proved to be normal. Osler's hereditary haemorrhagic telangiectases can also be excluded, for no sign thereof could be found.

All my haemorrhagic diathesis cases are clinically suggestive of essential thrombopenia, but they differ from it in that there was no relationship between the bleeding-time and the number of thrombocytes. The haemorrhagic diathesis in G. S. in family 2 is, however, an exception in this respect. As already pointed out, she is the maternal aunt of B. B. and S. B. in family 2. G. S. developed thrombopenic purpura at the age of 26 as a sequel to acute hepatitis. She has been well before and after this event. On account of the atypical behaviour of her case, it is conceivable that her haemorrhagic diathesis belongs to another group, but it is also possible that her reaction, evoked by acute hepatitis, was the expression of the same hereditary predisposition.

Among Glanzmann's cases there was one with a somewhat similar record. The child of a patient suffering from Glanzmann's thrombasthenia developed thrombopenic purpura as a sequel to measles and pneumonia, the blood returning to normal after these infections had passed off. One is tempted to assume that essential thrombopenia and haemorrhagic diatheses clinically suggestive of essential thrombopenia (thrombopenic and non-thrombopenic) may belong to a comprehensive, pathogenetically superior group of conditions which may be hereditary.

Our other patients had presented signs of a haemorrhagic diathesis since they were quite young, and the bleeding-time had been prolonged even when the number of thrombocytes had been perfectly normal. Thrombopenia is rare, and when it has been observed, it has not been associated with any increased tendency to bleeding. These haemorrhagic diatheses make one think primarily of constitutional thrombopathia of the v. WILLEBRAND—JÜRGENS type. Haematologically and clinically, the first patient, (K. I., family 1, pedigree 1) with a prolonged bleeding-time as the most important feature, conforms well to the v. WILLEBRAND—JÜRGENS type. In this case mucous membrane haemorrhages (nose-bleeding) was the most prominent feature as in the families on the Aaland Islands observed by v. WILLEBRAND and JÜRGENS. Haemorrhages into the skin, petechiae and ecchymoses did not figure prominently in these cases.

In two cases, one in each of the two last families (S. B. family 2 and K. H. family 3), reduced clot-retraction was observed even when the number of thrombocytes was normal. In this respect these cases also resemble cases of Glanzmann's thrombasthenia and the Naegeli type. But they lack the characteristic changes in the morphology of the thrombocytes as in Glanzmann's thrombasthenia and the Naegeli type. Unfortunately clot-retraction was not investigated in all our cases.

The haemorrhagic diatheses under discussion resemble one another clinically to such an extent that we may possibly be dealing with various manifestations of one and the same disease. On the other hand, we must keep in mind a fact, which clinicians are often liable to forget, that diseases resembling one another to such an extent that they are confused, one with the other, may be the outcome of different genes. Hitherto no connexion has been established between the two families investigated. But two of the great-grandparents of K. I. in family 1 on the father's side lived in the same County as several members of family 3. Some connexion between families 1 and 3, far back in time, cannot be excluded.

None of the pedigrees definitely indicate a dominant inherit-

After proof-reading: An existing relationship between family 1 and 3 far back in time has been discovered recently.

ance of these haemorrhagic diatheses. The pedigree of family 1 provides no information on the mode of inheritance, whether it is recessive or dominant. But in family 2 there is evidence in support of recessive inheritance in this that in family B. (to which the cases B. B. and S. B. belong) there occurred three cases of haemorrhagic diathesis in children whose parents were related to each other but healthy. This certainly indicates that the disease is due to a recessive gene.1 There is evidence in favour of recessive inheritance also in family 3. The parents of the 73-year old man L. Ø. were related to each other, but they are said not to have suffered from any haemorrhagic diathesis. These parents died long ago, and as they have therefore not been examined. The many cases in family 3 may be accounted for in this way that its members lived in a district in which consanguine marriages were comparatively frequent. Under precisely these circumstances conditions are favourable for the propagation of a recessive gene with a corresponding accumulation of homozygote individuals in a community (see Professor O. L. Mohr on Oligophrenia Phenylpyrouvica). This latter consideration is also one of the reasons why I cannot understand how Professor v. WILLEBRAND can claim that his pedigrees afford such definite evidence of dominant inheritance when we consider the point to which he himself has drawn attention, namely that consanguine marriages have taken place for centuries in the isolated Aaland Islands. In his pedigrees he has also classed as suffering from haemorrhagic diatheses persons who have suffered only from nose-bleeding and who have not been carefully examined.

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Endogenous haemorrhagic diatheses with prolongation of the bleeding-time, as in the cases just mentioned, have not hitherto been described in Norway. In the rest of Scandinavia only a few cases have been put on record apart from those recorded by v. WILLEBRAND (ANDREASSEN, BRUUN, JELKE and ROSLING). Once attention has been drawn to these cases, it is quite likely that they will prove not to be so very rare. It is important to note that these diseases may be responsible for simple nose-

¹ S. B. who had thrombopenic purpura when 26 years old may be homozygous too as her parents are related to each other.

bleeding or prolonged haemorrhage after the extraction of a tooth. Just before this article was completed, a new case of haemorrhagic diathesis with a prolonged bleeding-time as its most important feature was referred to me. The patient was a boy who had been admitted to an Ear, Nose and Throat Department for nose-bleeding, and to a Dental Surgery Department for haemorrhage after a dental extraction.

Treatment.

When haemorrhages have been severe and alarming, the treatment of these haemorrhagic diatheses has consisted of blood transfusions. No absolutely sure effect has been seen from bloodtransfusion in regard to haemostasis. Bloodtransfusion apparently does not act on bleeding-time, nor does it influence the tendency itself to bleed. In one of the cases just recorded (S. B. in family 2), the bleeding-time immediately before a blood transfusion was 15 min. It was examined again 3/4 hr. after the transfusion when it was found to be 30 min. This observation coincides with the experiences of MINOT and FOWLER in similar cases. We have not ventured to remove the spleen of any of the patients admitted to the Children's Department as experiences with similar cases have not been very encouraging. The patient reported on by LITTLE and AYRES died of haemorrhage as a result of the operation, and in the case reported by GIFFIN, that of a 9-year-old girl, the cutaneous haemorrhages ceased some time after the operation, but when she grew up she suffered from menorrhagia. In one of our own cases (G. S., family 2) the spleen was removed at a provincial hospital and, post or propter, she recovered after this operation. As already pointed out, it is possible that she belongs to another group of haemorrhagic diatheses. We have had satisfactory experiences with collodion, applied directly to a wound or on a bandage, when the lesion is slight, as for example, when the skin has been pricked in taking a sample of blood. Collodion forms a firm membrane which acts by strictly mechanical means in arresting a haemorrhage.

Summary.

The author has investigated the familial occurence of haemorrhagic diatheses with prolongation of the bleeding-time in three families.

The number of thrombocytes was, as a rule, normal. Thrombopenia (with the number of thrombocytes as far down as to 8300) was observed at certain of the examinations. Diminution of clot-retraction was also observed in some of the cases even when the number of thrombocytes was normal. In the second family a maternal aunt of children suffering from haemorrhagic diathesis with prolongation of bleeding-time, developed transitory thrombopenic purpura at the age of 26 as a sequel to an attack of acute hepatitis. She showed no tendency to bleed excessively either before or after this event. In the other cases there was no relationship between the number of thrombocytes and the tendency to bleed, and the thrombocytes showed no important departures from the normal. The coagulation-time and the prothrombintime were normal. The fact that several patients were the offspring of parents who were related to each other and who showed no signs of a haemorrhagic diathesis is suggestive of a recessive inheritance.

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Rheumatoid Arthritis in Children. A clinical study.

By

GUNNAR EDSTRÖM, M. D.

Sixty-five cases of rheumatoid arthritis, where the disease had started during the first 12 years of live, were treated at the Rheumatological Department of the University Hospital in Lund during the years 1936—46. In this group were then not included tubercular, luetic, gonorrheal, septic or other special types of arthritis as well as cases of rheumatic fever. On the other hand all cases of chronic arthritis of unknown etiology, whether they were of a more pure infectious nature — subseptic forms — or had more pronounced secondary reaction — hyperergic types —, as well as all cases of Still's disease, were included. Only those cases of chronic arthritis, in which the three characteristic signs — arthropathy, adenopathy and splenomegaly — were observed, were included and diagnosed under the name of Still's disease.

Differential diagnosis.

The Wassermann reaction was performed with negative results in all cases. No reason to suspect a gonorrheal infection was existing in any of the subjects. Sepsis was suspected in four cases with prolonged hyperpyrexia, but repeated blood cultures gave negative results.

One case was admitted to the Department during this time under the diagnosis of juvenile rheumatoid arthritis, where the clinical examination showed, that it was a case of acute hematogenous osteomyelitis with adjucent joint infection of the type, described especially by Robertson. This subject was not included.

Tuberculin examinations were carried out on all patients with Pirquet and Mantoux intracutaneous injections up to 1—3 mgr. All except 6 cases were negative. One subject was earlier tuberculin-negative but had got a positive tuberculin reaction after a previous Calmette vaccination. Three cases - 10-11 years old — reacted positively but showed no other signs of tuberculosis, neither by clinical or X-ray examination. One patient became tuberculin-positive while under treatment - a very interesting case for the study of the variations and the intensity of the allergic secondary reaction in cases of this type -, but the reaction in this case must be regarded as aspecific-hyperergic (the case is described in details on another place, see EDSTRÖM (2)). In one case, however, there were papulonecrotic tuberculides, phlyctenular keratitis and hilus changes similar to those in tuberculosis - tb-bacilli were, however, not showed in cultures taken from the ulcerations in the skin —, combined with arthritic processes in many of the larger and smaller joints with periarticular oedema, mowing pains and X-ray signs of light bone and cartilage destruction. Clinically this case can best be characterized as »Rhumatisme tuberculeux Poncet».

Thirteen (20%) of the 65 subjects — all of them tuberculinnegative — had come to the Rheumatological Department after having previously been admitted to and treated long times — up to two years — on Hospitals for surgical tuberculosis under the erroneous diagnosis of tubercular arthritis. Two of these cases had monarthritis (in the knee joint), the rest showed polyarticular processes. A specimen of the capsula of the joint had surgically been taken in all of them and by the histologically examinations showed no signs of tuberculosis but the picture that usually is to be found by rheumatoid arthritis.

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The differential diagnosis as regards rheumatic fever is difficult. Transition forms between rheumatic fever and rheumatoid arthritis are sometimes found in children as well as in adults. The clinical course is then usually the following: one or several

attacks of rheumatic fever (carditis, chorea, acute arthritis, nephritis, etc.) followed by another attack, more or less acute in the beginning, but changing slowly into a chronic type of arthritis. Renzalli has described a such case. In this series we have one.

Heredity.

In 17 cases (26 %) rheumatic fever or rheumatoid arthritis had occurred among the patient's nearest relatives — parents, brothers, sisters, grandparents. The father had been or was ill

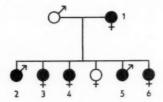


Fig. 1.

- 1 the mother of the patient, rheumatoid arthritis.
- 2 rheumatic fever 17 years old.
- 3 rheumatoid arthritis, beginning 20 years old.
- 4 rheumatoid arthritis, beginning 20 years old.
- 5 rheumatic fever, 11 years old.
- 6 the patient, rheumatoid arthritis, beginning 3 years old.

in 5 of these cases, the mother in 5. Two of the mothers were treated at the Department at the same time as their children, although they had not taken ill simultaneously. There are a brother and a sister in the series. They had taken ill at different times but at the same age (20 months). Their maternal grandmother and one paternal aunt had suffered from rheumatoid arthritis. In one of the 2 cases where mother and child were admitted into the Department simultaneously, the maternal grandmother had suffered from rheumatoid arthritis; in the other case two maternal aunts.

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In one of these cases the father as well as 2 of his brothers had contracted rheumatoid arthritis. In 2 cases the paternal grandmother was attacked, in one case the maternal grandmother, in another case both grandmothers.

One case in the series belonged to a veritable rheumatoid family (Fig. 1), and entirely corresponds to one observed by ROBECCHI & PESCARMONA, where 4 young brothers and sisters were attacked by rheumatoid arthritis.

Two of the children were one of binovular twins. In both cases the other twin was well.

The conditions of the children agree with those of adults (cf. Edström (3) and Robecchi).

Prodromes and precursory diseases.

In 3 cases the child fell ill in immediate connexion with preceding acute tonsillitis, in 3 after acute otitis, in 4 after sore throat or influenza, in 3 after scarlet fever, in one after measles, altogether 14 cases (22 %) in close connexion with infectious prodromes.

Gastro-intestinal disturbances were nowhere noted as prodromes, although observed by Coss & Boots in some of their cases. Neither were dental infections observed as prodromes (cf. COLVER).

Eight of the remaining cases fell ill after mechanical traumas — a hit or blow — on or near a joint. The injured joint was also first attacked by the process. In 4 of these cases, however, the child had had a sore throat shortly before this trauma (cf. Edström (5)).

One subject fell ill in direct connexion with a smallpox vaccination.

Forty-two subjects (65 %) became ill without any preceding infections or traumas. The percentage in a similar adult group was 73 % (Edström (4)).

In 2 cases the child had been troubled before by bronchial asthma and in 4 by eczema. One child had rachitis.

Age and sex.

Twenty-five of the 65 cases were boys (38 %) and 40 girls (62 %). Colver found in a similar series of 69 cases 25 boys

(36 %) and 44 girls (64 %) and Coss & Boots in a series of 56 cases 12 boys (21 %) and 44 girls (79 %).

When comparing with clinical records including all ages we find that of 1590 cases of rheumatoid arthritis treated in the pediatric, orthopedic, and internal-medicine Departments of the University Hospital in Lund during the years 1929—41, 86 (5 %) had fallen ill before the age of 15, 20 of which were boys (23 %) and 66 girls (77 %). Of 955 cases of rheumatoid arthritis, found in a field investigation in Sweden (Edström (1)) 66 (7 %) became ill before the age of 15, 19 of which were boys (29 %) and 47 girls (71 %). The girls seems to be more affected than the boys.

The age distribution of the 65 cases of the series is shown by the following diagram (Fig. 2).

This diagram agrees fairly well with the corresponding diagram of COLVER and COSS & BOOTS. In all these three series

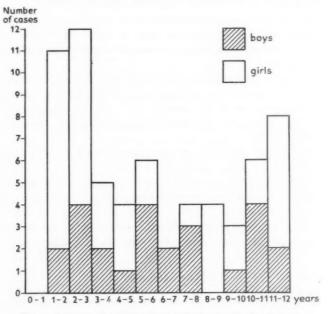


Fig. 2. The age distribution at the beginning of the disease.

the frequency is higher in the pre-school age, except the first year. No illness could be noted in these series during the first year of life, which agrees with Coss & Boots. Colver found 2 cases, however, and Holzmüller one. The youngest subjects in the present series were 2 girls, who were afflicted at 13 months of age, one girl who fell ill at 14 month and 2 at the age of 16 months. At the age of 18 months 1 boy and 2 girls became ill, at 20 months 1 boy and 1 girl and, at 21 months, 1 girl.

During the second and third years no less than 23 subjects became ill or 35 %. Most of these also were severe.

The cases near the age of puberty were often of a milder type—
the same observation has been made by LEONARD—and at the
beginning of the puberty a pronounced healing tendency is often seen.

The clinical picture.

Only 3 (5 %) of the 65 cases showed the clinical picture of Still's disease with arthopathy, adenopathy, splenomegaly, and hepatomegalia. Only one of these subjects had also pericarditis. Still's disease isn't a common form in this series. Wissler's series of 26 cases contains 3 cases of Still's disease. Seventeen of the 56 cases of Coss & Boots had splenomegaly and 13 hepatomegalia, 11 of the 39 cases of Holzmüller's he considers to belong to Still's type. Ibraham, de Lange and Rhonheimer have also noted a rather limited number of cases of Still's disease in their series of juvenile chronic arthritis.

Besides the 3 cases of Still's disease there was widespread lymphadenitis in 3 additional cases and less widely spread in 4 others.

Cardiac status. Twenty-nine subjects (45 %) had a more or less temporary myocardiac affection. In 8 of these cases the X-ray examination showed a dilatation of the heart as well as electrocardiogram-changes and physical pathological findings. In the remaining cases there were Ecg.-changes in the form of split Q—R—S-complex and extended P—Q systolic murmur or tachycardia. No heart block was evidenced. By way of comparison it can be mentioned that APPELGREN found similar

changes of the heart in 45 % in a similar group of adults with rheumatoid arthritis, and that Coss & Boots found such changes in 25 cases or 47 % of their child subjects (cf. also Kern).

The cardial lesions as well as the renal ones seem to be more common in rheumatoid arthritis than one has been led to believe as is shown by both the clinical findings and the post-mortem examinations (BAGGENSTOSS & ROSENBERG, KUHNS & JOPLIN, FINGERMAN & ANDRUS, PORTIS).

One of the cases of Still's disease is bed-lying in cripple-home in cardiac insufficiency. One of the cases developed a mitral vitium. The conditions of heart insufficiency in rheumatoid arthritis do not appear until after a period of illness of several years, however (Edström (8)). Therefore the time of observation is too short of this series to allow any evaluation of the frequency in the long run of such insufficiency in groups of this kind.

One patient had encephalitis with attacks of dizziness and restlessness, as well as temporary diplopia; one had iridocyclitis of both eyes with small synechias as well as small, fine precipitates; the patient also had conjunctivitis of the right eye. One patient had kerato-conjunctivitis sicca at the age of 13. Two patients developed, besides the iridocyclitis, also one-sided uveitis of a malignant character, which caused a considerably decreased sight of the affected eye (cf. Sorsby & Gormaz).

In adults iritis develops in about 2.5 to 4.5 % of cases of rheumatoid arthritis according to Berens et al. which agrees with the findings in our hospital.

Two subjects contracted hepatitis. One case was mild and passed off after about a fortnight. It appeared 4 days after the patient — aged 4 — had received the last of 3 intramuscular injections of Solganal-B-oleosum of 0.005, 0.01 and 0.02 g respectively; it probably has some connexion with the chrysotherapy. In the other case the hepatitis appeared 6 months after completed Au.-therapy as an acute infectious process; the patient died after about 3 weeks' illness. The liver showed upon autopsy pronounced inflammatory changes. The normal trabecular structure was dissociated by inflammatory exsudation and granular

tissue, spreading interstitially between the balks of the hepatic cells. The histological diagnosis was: chronic hepatitis overgoing to cirrhosis. It is not out of the question that this case was due to a delayed toxic effect of chrysotherapy, but it is more probable that it was a malignant infectious hepatitis — Weil's disease — death perhaps being caused by inferiority in the liver function, as a result of the patient's rheumatic affection. According to Robinson, however, no such inferiority in the liver function exists in rheumatoid arthritis.

In 3 cases transitory nephritic symptoms occurred with traces of albumin in the urine and red blood cells in the urinary sediment. In all these cases the symptoms appeared in immediate connexion with chrysotherapy which was being administered at the time, and it is therefore difficult to decide whether they are due to the original infection or to the toxic influence of this therapy.

The visceral lesions in rheumatoid arthritis have previously been rather underrated (e.g. Copeman). Baggenstoss & Rosenberg, Kuhns & Joplin and others have shown, however, that especially cardial and nephrogenous lesions appear quite often in obductions of such cases although the histological findings must be considered as non-specific. Baggenstoss & Rosenberg found low grade non-specific glomerulonephritis in 19 cases out of 30. On an after-examination of a series of 262 cases of rheumatoid arthritis in all ages 5 to 8 years after the treatment, this author could also demonstrate that 15 or 6 % had died with visceral lesions, most probably related to their rheumatic affection. Six cases died of cardiac failure and 5 of renal lesions, ending in uremia (one of them had amyloid degeneration) (Edström (8)). Renal lesions are not uncommon in rheumatoid arthritis.

Two cases developed pleural pneumonia. No case had amyloidosis.

All the cases evidenced a moderate hypochromic anaemia, but only 6 subjects had haemoglobin values below 60 %. Eosinophilia of over 4 % occurred in almost all cases, both in those subjected to chrysotherapy as well as the others.

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Fig. 3. Girl, 5 years. Duratio morbis 1 1/2 year. Rheumatoid arthritis, not Still's disease. Periarticular oedematic swellings and flexion contracture on right knee and right ankle. Restitutio ad integram.

Peritendinitic changes were observed in 8 subjects, 2 of whom had changes of the flexor tendons of the fingers (cf. conditions in adults, Edström (7)); bursitis occurred in one case and subcutaneous nodules in 3 others.

The arthritic syndrome began in 49 cases (75 %) in the lower extremities, i. e. in 26 cases (40 %) in one or both knee joints, in 17 cases in the tarsus or the talocrural joints, in 3 cases in both knee joints and tarsi, in 2 cases in the hip joint, and in 1 case in metatarsophalageal joints. In 7 cases (11 %) the arthritic syndrome started in the joints of the upper extremities, i. e. in 5 cases in the joints of hands or wrists and in 2 cases in one or more of the finger joints. In 1 case the arthritis began in the joints of the cervical vertebrae of the neck, in 4 cases simultaneously in carpi and tarsi, and in one case at the same time in one knee joint and one finger joint. In 3 cases, finally, the



Fig. 4. Girl, 3 years. Duratio morbis 1 year. Rheumatoid arthritis, not the type of Still. Periarticular oedematic swellings around the proximal fingerjoints II—V. Restitutio ad integram in these joints.

arthritic symptoms were so general from the beginning that it could not be decided in which joint or joints the illness began.

In 19 cases the process began as monarthritis during the first month of illness, thereafter attacking several joints. In 5 of these cases, all with gonitis, the process remained as monarthritis during the whole period of illness. By way of comparison it can be mentioned that 10 of the 39 cases of Holzmüller's were monarthritis, 7 of which had gonitis and 3 coxitis.

The arthritic syndrome started often in one or both knee joints and was as a rule most malignant in these joints. Many subjects were admitted with flexure contractures in these joints. Also talipes equinus and contractures in the hip occurred. When admitted to the hospital about half of the patients could not walk or stand on account of contractures in the joints of the lower extremities (cf. RODEN).

In 4 cases the processes in the finger joints resulted in a shortening of one or several fingers (cf. Coss & Boots).

In 1 case arthrotomy was performed on account of a free body in one knee joint. In the operation the joint cavity was observed to be almost entirely filled with firm fibrous connective tissue, covering the surfaces of both the femur and the tibia. The final result was a healing of the process in ankylosis. The patient is therefore considered imperfectly healed although he can run about fairly freely without pain.

Sedimentation-Rate (according to WESTERGREN).

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The 3 cases of Still's disease all showed a SR of about 100 mm per hour.

Five of the remaining 62 cases were admitted in a later phase with fully developed deformity of the joints; 4 of them were after a clinical examination immediately transferred to the orthopedic department.

The SR according to Westergren in the 57 other cases was generally high in the early active stage of the infection; some cases with a relatively normal SR were observed, however, — these cases all had shown pathological SR before admission. The distribution of the SR during the first time on the hospital was the following:

SR mm/per hour	Cases
under 12	5
12-20	13
21-30	3
31-40	8
41-50	10
51—100	15
101	9

On dismissal from the hospital the distribution was as follows:

SR mm/per hour	Cases
under 12	30
12	5
13—20	5
21-30	8
31-40	3
41-50	2
51-60	1

and 3 of the cases are still in the hospital.

Serological reactions and throat tests.

Antistreptolysin titration according to WINBLAD was performed in 23 of the cases. Of these 6 gave a maximum value of 100 E., 2 showed values between 100 and 200 E., and the remaining 15 cases, or approximately $^2/_3$ of the total number on which this titration was carried out, showed values of at least 200 E. and 3 of these cases gave minimum values of 1 000 E. In one case where the ASL titre was negative the antifibrolysin titre was positive.

Agglutination for haemolytic Streptococci according to Kalbak was performed in 17 cases. Of these 9 were negative, 7 positive, and one gave border-line values.

Throat tests for haemolytic Streptococci were carried out in 32 cases. Fifteen subjects gave positive results and 17 negative. In one of the negative tests a growth of Streptococcus viridans was observed.

No positive tests (ASL, Aggl., Throat) were found in the cases of Still's disease.

Relapses.

In 13 of the cases (20 %) the joint condition was recurrent. Seven of these patients were treated during the *first* attack. 3 of them were also treated during the second attack which was not followed by further attacks. The 4 other cases experienced only mild recurrent attacks which did not require hospital treatment.

Four patients were at first treated during the second attack. One of these suffered a third attack which was also treated.

Two patients were treated during the *third* attack. No further recurrences were noted in these cases.

All of these relapses except one are now completely recovered.

Therapy.

 $Group\ A.$ Four of the 65 cases were upon admission in a relatively healed infectious state but with crippled and contracted joints in need of primarily orthopedic treatment. After clinical examination they were transferred to the orthopedic department.

The remaining 61 cases were treated in the hospital for an average of 216 days per patient and 137 days per visit.

Group B. Five of these patients were relatively mild and early cases. They were admitted before they had had the illness for one year. They were treated with rest, thermotherapy, medical movement treatment of the joints, salicylic acid, and vitamines. Mild and temporary relapses occurred in 2 cases.

Group C. Fifty-one of these cases were bedridden for a long time and received thermotherapy (usually mud packs around the diseased joints 2 or 3 times a week), medical movement treatment in addition to the usual conservative orthopedic therapy (plaster, splints, stretching apparatus, etc.), salicylic acid (in some cases amidopyrine), vitamins, and gold therapy. Temporary relapses occurred in 3 cases.

The gold preparation which has been used in all cases was in oil-suspension: Solganal-B-oleosum (Na-Au-thiogluconate) during the first 9 years until the end of 1945 and Myoral (Ca-Authiogluconate) during the last 2 years were injected intragluteal every 4, 5, or 6 days beginning with an initial dose of 0.005 or 0.01, which was slowly increased to 0.05—0.07—0.10 g. The dosage as well as the interval between injections were determined by the body weight of the child. The number of injections in each series was usually 12—15, sometimes more and sometimes less, depending upon the clinical reaction of the patient. The total dosage per injection series was approximately 3 cg. Solganal-B-oleosum or 2 cg Myoral per kg body weight. In five of the cases the treatment was interrupted because of complications.

At the same time the patients have regularly received salicylic acid: children whose body weight was less than 20 kg received 0.50 g thrice daily; older children received a larger dose up to 1 g three times a day for those who weighed more than 40 kg. In some cases amidopyrine was used instead of salicylic acid. 0.10 g 5 times a day for children under 20 kg and corresponding doses for older children in relation to their body weight. The patients have also regularly received codliver oil and vitamin B and C preparations.

Group D. The remaining 5 cases received the same therapy as the preceding group except the Au.-therapy. One of them was remitted from another hospital, where the patient has received Au.-therapy and developed a dermatitis. Afterwards the patient healed. One subject was admitted in an advanced stage with a practically healed infection and received mainly movement treatment of the joints. The final result was defective healing. One case — a 2-year old girl — arrived with acute gonitis, subfebrile and with high SR. She healed rapidly when treated with salicylic acid and vitamins as well as physical therapy. One case was treated with sulfadimin instead of Au.-therapy with good effect and was healed. Another patient with a very malignant case of Still's type had on admittance lain highly febrile for more than 1 year - except for shorter periods - and was in poor general condition. The patient was treated with general thermotherapy in the climate laboratory (see Edström (6)) and was restored to health. After returning home the patient relapsed, and was re-admitted. This time the patient could not be treated with the same good effect and is to-day bed-lying in cardiac insufficiency in a cripple home.

Observed complications in the Au.-therapy.

One case was admitted with dermatitis after Au.-therapy. Among the 51 cases which were treated with Au in the hospital the following complications were noted simultaneously with this therapy and most likely caused by it:

- 3 cases of *dermatitis*, lasting 2—5 weeks, all of which showed eosinophilia, 39, 21, and 16 % respectively. Two had red blood cells in the urinary sediment,
- 2 cases of febrile reaction together with exacerbation of the joint process and isolated red blood cells in the urinary sediment,
- 3 cases of gastro-enteric inflammation accompanied by vomiting attacks, nausea, and slight diarrhea (the last mentioned in two cases). Two subjects also had aphtae,

1 case of nephritic inflammation with temporary albuminuria and red blood cells in the urinary sediment,

1 case of hepatic inflammation with jaundice for 2 week s.

A total of 10 cases (20 %) with complications.

In 10 other cases eosinophilia was noted of at least 15 %, 7 of which had at least 20 %, and in another 6 cases eosinophilia between 10 and 15 %. If this eosinophilia is considered as a Au.-reaction — which is open to discussion — reactions of the above-mentioned kind occurred in 26 cases or in about half the cases.

No case of granulocytopenia or thrombocytopenia was observed. All the reactions mentioned above were mild and passed off rapidly. In this connexion, however, the patient should be mentioned (see Page 340), who died in hepatitis ca 7 months after the discontinuance of the Au.-therapy and where the possibility of an Au.-intoxication cannot be disregarded.

The kinesotherapy of the joints.

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Rheumatoid arthritis in children has a greater tendency of causing contractures in the joints than in adults. They appear as a rule rather slowly but may sometimes arise during the course of one night, which fact can be attributed to the hyperergic character of the damaged rheumatic tissue (KLINGE, BAGGENSTOSS & ROSENBERG). These contractures are sometimes flexible but as a rule rather hard and difficult to treat and demand therefore a careful supervision from the start with regard to the function of the joint. This is especially valid for those who are admitted into hospitals. The rigid schedule which often predominates there has the effect that the patient uses his joints less, causing severe states of contractures, which, if allowed to remain for some months, can make the patient an invalid for life, even through the infection may heal after all.

As mentioned above the joints of the lower extremities in children are attacked more often and more seriously than in adults. The most common contractures are muscular contrac-



Fig. 5. Plaster circular bandage for extension. Is kept seven days, after that changed to a splint and cautious movement is given daily. — The boy had had a severe contracture of the knee.

tures in the knee joints, sometimes combined with muscular contractures also in the hip joints. A large per cent of the present group has arrived at the hospital with such contractures and unable to stand or walk.

The kinesotherapy of the joints, which was begun at the same time as the internal therapy, has aimed at overcoming these flexion contractures, permitting full stretching and enabling the patient to stand and walk. The active movement treatment is very important and must be used even in febrile conditions daily, although with the greatest care. Sandbags are used in mild cases of flexion contractures. They are warmed before usage and placed above the knee joint with the lower part against the upper edge of the patella as well as below this joint with the upper part against the lower edge of the patella, for 15—30 min., 2 or 3 times daily. These sandbags should not be placed on the patella, as the sensitiveness for pressure over the joint itself is often considerable.

The most common aid in the kinesotherapy is, however, so called pin-tractions (Fig. 6) which are applied for a period of some weeks. In order to prevent the patient from being drawn towards the foot of the bed, that part of the bed is elevated with blocks so that the body-weight of the patient acts as a counterbalance.





Fig. 6. Treatment of flexionscontracture of the knee with continuous draught.

Circular plaster-of-paris bandages are used only in more severe contractures or in cases where the joint on account of a highly destructive process in bone and cartilage is considered to require absolute rest for some time. These are placed in extreme traction to serve as extension treatment at the same time. This fixation is — if no highly destructive process — not allowed to remain for more than 7 to 10 days.

It is also important to control the function of the foot joints. Talipes equinus develops easily. In order to avoid this hard kicking cushions are used at the hospital. It is also important that the beds are not too long and that there is no pressure of heavy bed-clothes on the feet. If talipes equinus has developed, the construction on Fig. 9 is used as auxiliary apparatus in the movement treatment.

Considerable difficulty arises when these small patients are to be taught to walk. Many of them are so young that they have never learnt it properly before they became ill. Go-carts of varying types for various ages are then of great value (Figs. 7—8).

Specially built orthopedic shoes are often required when the process in the foot joints has been of serious nature.





Fig. 7. Go-cart for children of 2-4 years.

Fig. 8. Go-cart for children of 5—10 years.



Fig. 9. Band of iron for treatment of pes equinus artriticus.

The tendency of contractures in the upper extremities is not so pronounced in this group. Sometimes it may be necessary even in children to use fixation splints of light metal or plaster on the wrists in order to avoid a volar contraction.

Results and prognosis.

Information was obtained concerning all the patients in an after-examination at the turn of the year 1946/47.

The 4 cases belonging to Group A showed: 1 invalid in bed, 2 crippled and imperfectly healed, receiving education on homes for crippled and, finally, 1 imperfectly healed but in such condition, that she can go in usual school.

All 5 cases in Group B were shown upon after-examination to be completely cured without defects.

Among the 51 cases in Group C 34 were found upon afterexamination to be completely cured without defects. Three of these subjects had relapses after the first treatment but were completely healed after this recidivation. Fourteen cases were still going on or were partially cured; two subjects had become invalids and there was one death due to hepatitis.

In Group D 3 cases were cured, one was partially cured, and one is lying in cardiac failure.

Of the 3 patients with Still's disease all are invalids. Five cases had existing joint deformations already upon admission to the hospital.

Among the remaining 57 patients, who came to the hospital before such deformation of the joints had taken place, 42 cases (74%) were cured without defects. Thirty-five patients of the 52 (67%), who had undergone gold therapy — 51 on the Department, 1 before — were on after-examination found to be healed without defects (cf. Sundelin).

Among the 30 patients who had been afflicted with the disease for less than a year before admission to the hospital 25 (87%) were shown on after-examination to be cured, 3 were still ill, one was an invalid, and one had died (hepatitis case).

Among the 17 patients who had had the disease for between one and 2 years before admission 11 (65 %) were found upon after-examination to be cured, 3 were still ill or partially healed, 3 were invalids.

Among the 18 patients who had been afflicted with the

disease for more than 2 years before admission 7 (39%) were shown upon after-examination to be cured, 9 were still ill or partially healed, and 2 were invalids.

The prognosis consequently appears to be better for those who have had the disease only a short time before admission.

The duration of the disease for the 31 cases who were completely cured after the first attack without relapse was in no case less than one year: in 6 cases it was approximately one year, 3 cases ca $1^{1}/_{2}$ years, 10 cases ca 2 years, 3 cases ca $2^{1}/_{2}$ years, 5 cases ca 3 years, 3 cases ca 4 years, and 1 case between 5 and 6 years. The average duration of the disease in these cases was approximately $2^{1}/_{2}$ years.

Discussion.

Rheumatoid arthritis occurs not infrequently in childhood. Incipience is usually, especially during the second and third years. Girls are afflicted more often than boys. The form of this disease known as Still's disease seems to be less common in Sweden.

The onset of the disease in children differs from that in adults in that the larger joints are more often attacked. The process frequently begins as a monarthritis and shows this clinical picture now and then throughout the entire course of the disease. The joints of the lower extremities are usually affected, especially the knee joints. This condition is possibly the reason why the disease in the preliminary stage is often wrongly diagnosed as tubercular arthritis.

When an arthritic process occurs in children in the pre-school age a tubercular test should be made. If the patient is tuberculinnegative this does not mean that the process sure is non-tubercular (Heduall), but the great possibility of the condition being a rheumatic process should be considered. Children with tuberculin-negative arthritis should not be placed in a tuberculosis sanatorium, unless the diagnosis of tuberculosis has been definitely established by another means.

The clinical onset of chronic arthritis, with the exception of Still's disease, is in the majority of children similar to that in adults. Besides the arthritical symptoms it begins insidiously with subfebrile temperature, moderate increase in the SR and moderate hypochromic anaemia. Symptoms of visceral lesions occur more infrequently except for signs of myocardial injury as seen in Ecg.-changes in the form of split Q—R—S-complexes and prolonged P—Q, systolic murmurs or tachycardia which are present relatively often even in the early stages. X-ray manifestations of dilatation of the heart generally becomes evident first in the later stages. As in adults there are sometimes peritendinitis and subcutaneous nodules. Iritis, iridocyclitis and retinal processes occur which can permanently affect the sight. Eosinophilia is common.

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The tendency towards muscular flexion contracture on the diseased joints is often marked, especially when the lower extremities are involved. The movement treatment of the joints is an important part of the therapy in avoiding defects and a more or less high degree of limited joint function as a lasting effect of such an arthritis.

In addition to physical therapy internal anti-infectious therapy is also important because of the often malignant and pronounced infectious character of the disease, in this series most gold therapy. Combined with that is given salicylic acid (or amidopyrine) for the purpose of decreasing the hyperergic reaction of the tissues.

The prognosis appears to be relatively good when such therapy is administered; approximately $^3/_4$ of the cases admitted to the hospital before deformation of the limbs has taken place have been cured. The exceptions are those cases of Still's disease where the prognosis is poor.

The duration of the disease is on the average from 2 to 3 years for those patients who are cured. Cases of longer duration occur but usually lead to complete invalidism. When the patient is not healed within the first 3 or 4 years the prognosis generally is poor.

Summary.

Rheumatoid arthritis occurs not infrequently in childhood. Girls are afflicted more often than boys. The form known as Still's disease seems to be less common in Sweden.

The onset of the disease in children differs from that in adults in that the larger joints are more often attacked. The joints of the lower extremities are usually affected, especially the knee joints. The process frequently begins as a monarthritis. In preliminary stage it is often wrongly diagnosed as tubercular arthritis.

Besides the arthritical symptoms it begins insidiously with subfebrile temperature, moderate increase in the SR, moderate hypochromic anaemia and signs for myocardial injury. X-ray manifestations of heart-dilatation generally becomes evident first in later stages. Sometimes peritendinitis and subcutaneous nodules. Processes in the eyes occur. Eosinophilia is common.

The tendency to flexion contractures is often marked. The movement treatment of the joints is an important part of the therapy in avoiding defects. Internal anti-infectious therapy is also important because of the often pronounced infectious character of the disease (gold-salts or sulfonamides-preparations). For decreasing the hyperergic reaction of the tissues salicylic acid or amidopyrine is given.

The prognosis appears to be relatively good — except of the cases of Still's disease. The duration of the disease is on an average from 2 to 3 years for those patients who are cured. Protracted care on hospital is necessary, preferably on arthritic clinics.

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Syndrome extra-pyramidal consécutif à un ictère généralisé de type familial (maladie de Pfannenstiel).

Profil neurologique et psycho-dynamique.

Par

M. SCHACHTER.

Le problème des ictères généralisés, grâves, de type famílial est, malgré les nombreuses recherches, très compliqué. Il est, toutefois, évident que les relations sont étroites entre l'ictère grâve familial (maladie de Pfannenstiel), l'anasarque foetoplacentaire avec érythro-leucoblastose (type Schridde), l'ictère nucléaire (»Kernikterus» d'Orth-Schmorl) et l'anémie du nouveauné, à caractère familial, d'Ecklin.

Tout en soulignant l'extrême gravité quoad vitam, de tous ces tableaux cliniques, les auteurs décrivent, de plus en plus fréquemment, des cas de survie. Ces derniers ne manqueront pas de devenir plus fréquents, et ce, grâce aux considérables progrès réalisés, par les recherches immunologiques inaugurées par LEVINE et Stetson, confirmant l'existence, chez l'homme, du facteur sanguin Rh (LANDSTEINER et WIENER). Effectivement, des travaux cliniques mettant en évidence le rôle décisif (dans la pathogénie des syndromes ictériques grâves et des érythroblastoses du nouveau-né) du facteur Rh-négatif dans le sang maternel, ont ouvert la voie à des thérapeutiques rationnelles qui - à l'avenir — sauveront, peut-être, tous ces enfants, autrefois voués, en majorité, à une mort certaine. (Nous faisons allusion, avant tout, aux transfusions chez le petit malade, de sang Rh-négatif. On sait que dans environ 90 % des cas, ces enfants sont Rh-positif, alors que leurs mères sont Rh-négatif: B. Broman, 1944. De même,

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ce dernier auteur se demande si l'utilisation d'hormones — la progestérone, par exemple — n'est pas promise à des succès indéniables.)

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Mais revenons à notre point de départ. Des cas authentiques de survie ont été publiés, chez des enfants ayant été atteints d'ictère généralisé, grâve, familial, ou de sa complication neurologique, dite »ictère nucléaire».

Chez nous, le professeur M. Péhu en collaboration avec A. Brochier, a précisé — dans plusieurs travaux cliniques et hématologiques — que l'existence certaine de maladie de Pfannenstiel ne doit être admise que si l'on a affaire à un syndrome clinique caractérisé (ictère grâve, prolongé, érythroblastose) évoluant selon le mode familial.

Dans notre cas personnel, il s'agit, évidemment, d'un diagnostie rétro-spectif (tout comme dans le travail, si important de Mme le prof. C. DE LANGE, 1936). Il n'est pas question de démontrer l'érythroblastose chez notre sujet. Par contre, le contexte clinique, anamnestique et évolutif, nous autorisent à rattacher—sans hésitation—à une maladie de Pfannenstiel avec syndrome d'ictère nucléaire consécutif, guéris, le tableau neuro-psychopathologique que, présente notre malade.

Voici, d'abord, résumée, cette observation:

Obs. no. 2392. Bi . . For . . , est âgée actuellement de 15 ans. Nous la connaissons depuis 3 ans, mais l'observation et l'étude détaillée est récente.

Ses parents, gens intélligents et instruits, sont en bonne santé. La grossesse de Bi.. a été sans incidents dignes de remarques.

Enfants: a) un garçon, naissance normale; a présenté une jaunisse intense mais soigné, il a survécu. (Nous n'avons pas plus de précisions.) b) Le sujet (voir détails plus bas). c) Une fillette, décédée le 10e jour après sa naissance, étant atteinte d'up ictère très intense, progressif.

Bi.. (2e enfant) est née environ 3 semaines après le terme normal (selon les déclarations de sa maman, une bonne et intelligente éducatrice). L'accouchement a été incidenté; on a dû appliquer le forceps et la ranimer. Le traumatisme obstétrical, doit donc être mentionné. Ajoutons encore un élément exogène insolite: à la veille de l'accouchement, la mère a été victime d'une intoxication alimentaire: la bonne avait mis, criminellement ou par sottise, des têtes d'allumettes dans une sauce qu'on a consommée quelques heures après. — L'ictère s'installa, chez

cet enfant dès la naissance, et se fonça de plus en plus progressivement (ses urines étaient noires-brunes). Vers le 10e jour, l'enfant a été »suprise» présentant des convulsions des globes et des membres. Selon les dires de la mère, ceci n'est survenu qu'une seule fois. (Nous avons des raisons de croire que d'autres ont certainement dû passer inaperçues.) L'enfant a été soignée, aussi vigoureusement que son frère ainé, atteint nous l'avons vu, egalement d'un ictère intense à la naissance avec, entre autres, des préparations de citrate de Na, des préparations homéopathiques et ce n'est qu'après 3 mois, qu'elle reprit son poids de naissance (4500 gr). A la suite des convulsions et de l'épisode ictérique, l'enfant avait présenté une »impotence» motrice du côté gauche. Un confrère compétent avait, effectivement, attiré l'attention des parents sur une hémiplégie gauche, plus accentuée au niveau du membre inférieur.

Premier développement: dentition à 8 mois (normale); marche: vers 17 mois sous forme »d'essais», mais ce n'est qu'à l'âge de quatre ans que la marche fut normale, sans appui. Parole: vers l'âge de 18 mois, mais en fait il ne s'agissait que de queluqes mots faciles, on ne comprenait pas ce qu'elle disait. Propreté sphinctérienne: acquise assez tôt (avant l'âge

de 3 ans).

Maladies infantiles: rougeole vers 7 ans, sans complications nerveuses évidentes. Varicelle, non compliquée neurologiquement, vers 4 ans.

A été placée, vers l'âge de 4 ans, dans une institution pour enfants retardés »parceque, nous dit sa mère, on ne comprenait pas ce qu'elle disait et qu'elle traînait sa jambe gauche et tenait son membre gauche accollé au thorax». Quand elle riait, ou pleurait, nous précise sa mère, elle présentait un rictus du visage dirigé vers le côté gauche.

Est amenée à nos consultations spéciales pour rééducation de la parole où elle suit — depuis très longtemps déjà, — des cours d'ortho

phonie.

Son trouble de l'élocution est très complèxe. Il s'agit d'une dysarthrie spasmodique, saccadée, avec une tonalité très aiguë, due — à notre avis —

à l'adjonction d'une importante hypoacousie bilatérale.

Examen: Sujet de constitution musculo-adipeuse moyenne. Squelette des membres normal. Colonne vertébrale: scoliose dorsale droite, lombaire gauche, avec scapulum alatum et légère tendance à la chute de l'omoplate dr. Crâne: normal. Squelette facial: régulier. On note une certaine hyperlaxité des coudes. Appendice xyphoïde non-palpable. Pas d'auriculaire infantile. — Cavité buccale: voûte ogivale. Quelques caries dentaires mais absence de stigmates spécifiques. Pas de signe de Chostek.

Viscères: poumons, coeur, rate et foie: rien d'anormal à signaler.

Thyroïde: non palpable. Organes génitaux externes: normaux. Pilosité axillo-pubienne; bien developpée pour son âge. Glandes mammaires bien constituées; mamelons ombiliqués. A été réglée à 14 ans.

Durée: 3 jours, non-douloureuses, peu abondantes. A présenté, sans cause évidente, une période d'amenorrhée du 6 mois. Nous l'avons soumise à un traitement adéquat.

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Examen neurologique: Bi, est du point de vue moteur, dans un état de quasi instabilité permanente. Les muscles de visage grimâcent sans cesse, ce ne sont pas des tics, à proprement parler. Ce sont des contractions des orbiculaires, des lèvres, des joues, des mâchoires. Les membres superieurs présentent des mouvements athétoïdes typiques. Durant les actes spontanés, les syncinésies d'association sont d'une intensité remarquable. Pendant le geste de rire, les traits sont tirés nettement vers la droite. Les réflexes des membres sont très vifs, mais égaux. Leur zone réflectogène n'est pas augmentée. On ne trouve pas de Babinski. Lors de l'épreuve des bras tendus, on note un écartement avec instabilité des doigts, chute du bras. La fermeture des yeux ne modifie pas, de façon manifeste, ces petits signes d'instabilité avec athétoïdisme digital.

Force des segments: dynamométrie à droite 15, à gauche 15 également.

Epreuves cérébelleuses: index-nez: hésitation légère; la diadococinésie est assez insuffisante des deux côtés. Le signe de Stewart-Holmes est pratiquement négatif. Romberg: absent.

Moşilité faciale volontaire: froncement des frontaux égal des deux côtés. La marche est plutôt lente, hésitante, mais nous devons compter avec l'existence d'un pied plat bilatéral.

Réflexes oculo-pupillaires: pupilles égales, régulières et contractiles à la lumière et à l'accommodation. Pas de nystagmus. Pas de modification dans la motilité extrinsèque des globes.

En somme, chez cette fillette qui a présenté — comme son frère aîné et comme sa soeur, décédée à 10 jours après la naissance — un ictère généralisé avec des troubles neurologiques (convulsions, hémiplégie gauche), nous constatons, à l'âge de 15 ans, l'existence d'un syndrome neurologique extra-pyramidal à type d'athétose bilatérale avec dysarthrie spasmodique complexe, syncinésies nombreuses et instabilité psycho-motrice. Ajoutons également, comme élément qui aggrave sa perturbation linguistique, un certain degré accusé d'hypoacousie.

Cette fillette a subi, nous l'avons vu, un important traumatisme obstétrical (forceps). Elle ne présente pas des stigmates squelettiques d'infection syphilitique congénitale.

Psychiquement, elle est lente. Les progrès scolaires et ortophoniques sont satisfaisants. Nous l'avons soumise au test de Rorschach, afin de mieux nous rendre compte de sa structure psycho-dynamique profonde.

(Nous utilisons les désignations françaises, d'après Mme Loosli-Uster, de Genève); G = perception globale; D = détail; Dd = petit détail; Dbl = détail intermaculaire; F% = pourcentage des *bonnes* formes; K = perceptions kinesthésiques; FC = perception de *formecouleur*; An% = pourcentage des perceptions *animales* (index de stéréotypisation).

Bi.. nous donne en 32 minutes, 41 réponses, ce qui est, pratiquement normal. Voilà quelques détails de son protocole:

G	1	F + = 15	An.	21, soit 51 %
D	18	$F \pm = 9$	Géogr.	7, soit 17 %
Dd	17	F - = 12	Hommes	7, soit 17 %
Dbl	5	F% = 54 %	Anat.	3
	A0.000	K = 2	plante	1
	41	FC = 3	aliment	1
			points	1

Type de perception: (G)—D—Dd—Dbl

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Type de réaction: 2 K/3 FC, soit 2/1,5, soit coartativité. Succéssion: plutôt relâchée, avec une note d'indolence,

Ce protocole, nous permet de tirer les conclusions suivantes; a) Le fait de donner, à son âge, 1 seul G, comme 2e réponse à la pl. V (elle dit: »une peau de lapin, avec pattes, oreilles»: G-F + An) est significatif pour son profil intellectuel modeste. Effectivement, le G est mal vu: on ne peut pas dire que Bi . . a été capable de donner la réponse »vulgaire», habituellement vue à cet âge. La grande proportion des D, Dd et Dbl, permet de préciser qu'il s'agit d'un esprit borné, puérilement méticuleux (»nörglerisch» d'après H. Rorschach), chose qui est corroborée par son bas pourcentage de F% 54, qui la classe parmi les débiles légères. Par ailleurs, la note de relâchement dans la succession de ses perceptions est un argument de plus. b) Son type de réaction, nous la montre comme une coartative; elle donne deux kinesthésies de type puéril, assez estompées par ailleurs. Elle ne réussit pas à formuler une pensée »mouvementée», il nous a fallu deviner le mouvement. Effectivement, elle donne, à la pl. III: »un petit bonhomme» et à la pl. IX, également: »un petit bonhomme de neige» (en position horizontale, en rose). Les 3 FC sont les seules »vibrations» de son affectivité réduite. Ainsi, le type de réaction souligne ce que l'on désigne si bien - chez ces types - comme coartativité avec indolence affective. Mais Bi.. nous a donné un très grand nombre de Dbl (détails intermaculaires) qui soulignent une forte tendance à l'opposition, à l'entêtement. Ceci cadre bien avec son caractère »difficile». c) Au point de vue du contenu des réponses, nous notons que son index de stéréotypisation (An % 51) n'est pas anormal. Mais, ce qui nous a surtout frappés ce sont les réponses suivantes qui montrent, de façon évidente, une contamination mentale, à caractère obsédant en quelque sorte, en relation avec son gros défaut d'articulation. Effectivement, nous avons relevé:

pl. II: »bouche ouverte» (extrem. lat. noire): Dd F- Hd

pl. III: »une petite bouche» (Dbl entre »panier»): Dbl F ± Hd

pl. VI: »le fond de la gorge» (milieu haut): Dd F + Anat.

pl. X: »la trachée artère» (milieu haut): D F + Anat.

C'est à sa pauvreté mentale que sont dues les nombreuses perceptions animales, la majorité se rapportant non à des animaux entiers, mais à des parties seulement.

En somme, le test psychodiagnostic nous montre que du point de vue psychodynamique, nous nous trouvons en présence d'un sujet peu doué intellectuellement; affectivement, elle est inhibée, coartative, comme sont les enfants conscients d'un défaut psychosomatique (dysarthrie, dans son cas); elle est aussi une instable et caractèrielle, opposante. Enfin, son défaut phonétique se réflète — à notre avis — manifestement dans son protocole psychodiagnostique. Ceci méritait, nous le pensons, d'être souligné d'autant plus que nous ne connaissons aucun travail rorschachien dans un syndrome neurologique extra-pyramidal associé à une dysarthrie accusée.

Il n'est pas dans notre intention d'étudier de façon détaillée les troubles neurologiques présentés, tardivement, par les enfants qui ont survécu à un ictère grave, familial avec ou sans syndrome d'ictère nucléaire surajouté. Nous nous contenterons seulement de quelques citations, sans avoir la prétention d'épuiser le sujet. (Nous reconnaissons volontiers cette lacune, mais les conditions actuelles nous empêchent encore de posséder — comme nous l'aurions voulu — toute la bibliographie de la question.)

Chez les enfants ayant, victorieusement, subi un ictère grave familial, Arkwright (1902), Pitfield (1912), Guthrie (1914), Spiller (1915), ont signalé, l'existence — comme dans notre cas — d'un syndrome extrapyramidal (pallidal, strié ou striopallidal) accompagné d'un état spasmodique des membres, débilité motrice et intellectuelle, arriération mentale. Le sujet étudié par le prof. A. Aritzia (Santiago de Chile, 1927 et 1934),

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présentait une forte surdité, des grosses perturbations de la parole et une démarche ressemblant à la maladie de Little. Le malade de M. Braid (1932), ne pouvait pas rester debout, mais son psychisme était intact (il est vrai, que dans ce cas, on avait mis en évidence des lésions osseuses de type kystique). Ce dernier auteur mentionne deux autres cas, ayant présenté une diplégie avec déficience mentale.

Chez les enfants ayant présenté un ictère nucléaire au cours de leur ictère grave, on a signalé, à peu près, les mêmes perturbations nerveuses. Ce sont, souvent, des arriérés. Leur developpement moteur est déficient. Le langage lent à s'établir et souvent, il reste, incomplet. La marche est, elle aussi, défectueuse. Souvent, il s'associe à ces signes, un état spasmodique (comme plus haut) rappelant la maladie de Little.

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Il est aisé de constater combien ces données sont corroborées par l'analyse symptomatique de notre malade. Ajoutons, une fois de plus, que l'analyse psychodiagnostique au moyen du test de Rorschach (premier document, à notre connaissance, dans ce sens) confirme et nuance encore mieux le profil somato-psychologique compliqué de ces sujets.

Mais, nous dira-t-on, le traumatisme obstétrical, ne doit il pas être incriminé dans le déterminisme des troubles neurologiques survenus après la naissance d'abord, et tardivement ensuite?

Pour M. Péhu, qui résume son opinion et celle d'autres auteurs, le rôle de cet élément ne doit pas être pris en considération. On peut . . . sans crainte d'erreur, l'éliminer . . . le problème n'est pas uniquement obstétrical; au fur et à mesure que progresse la connaissance des faits, il devient un problème génétique» (M. Péhu et A. Brochier, page 25).

En ce qui nous concerne, ayant consacré un important mémoire à l'étude du profil neuro-psychologique des traumatisés obstétricaux, nous avons montré, en nous appuyant sur un matériel de 353 cas de traumatisés crâniens que le pourcentage des encéphalopathies consécutives (3,39 %) n'était pas plus significatif que celui de 100 sujets témoins (3,00 %) »difficiles et caractériels, non traumatisés à la naissance. Aussi, ce fait nous semble-

t-il confirmer l'opinion de M. Péhu. — Nous nous garderons, toutefois, de trancher de façon définitive cette question.

Il résulte, donc, que c'est à l'ictère grave familial d'une part et à sa complication particulièrement redoutable qu'est l'ictère nucléaire, que sont dûs les troubles neuro-psychologiques décrits par les auteurs, et que nous avons retrouvés chez notre malade.

Le traitement de ces séquelles neuro-psychologiques est — on le sait — des plus difficiles. Les sédatifs nerveux, les modérateurs de la spasmodicité extra-pyramidale (préparations atropiniques, scopolamine), le calcium, les hormones, la rééducation motrice (gymnastique rationelle, mécanothérapie) linguistique et respiratoire, sont, en gros, les moyens dont nous disposons actuellement et qu'il faut savoir proposer et appliquer. Nous ne partageons pas l'optimisme de certains auteurs laudateurs de la di-électrolyse ou ionisation transcérébrale calcique.

Résumé: Description neurologique et psychologique d'un cas de syndrome extra-pyramidal à type d'athétose, chez une fillette ayant subi une atteinte d'ictère généralisé prolongé (de type familial, maladie de Pfannenstiel) avec syndrome d'ictère nucléaire consécutif.

Traumatisée de naissance (forceps), elle est le 3-e sujet d'une famille saine en apparence, atteint d'un ictère généralisé grâve à la naissance. Le 3-e enfant a, d'ailleurs, succombé, le 10-e jour, à cette maladie.

Ces cas ne sont pas nombreux, d'où l'intérêt de notre malade. De plus, nous avons pu pratiquer un examen psychologique au moyen du test psycho-diagnostic de Rorschach, qui nous a permis de penétrer mieux dans la structure intime de cette petite malade, caractérielle, instable-entêtée, affligée de gros troubles (cérébrogènes) du langage.

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FROM THE PEDIATRIC UNIVERSITY CLINIC, AARHUS (CHIEF PHYSICIAN: PROFESSOR BENT ANDERSEN, M. D.) AND THE INSTITUTE OF NORMAL ANATOMY OF THE UNIVERSITY OF AARHUS (CHIEF: PROFESSOR LARUS EINARSON, M. D.).

A Case of Arthrogryposis Multiplex Congenita Anatomically Appearing as a Foetal Spinal Muscular Atrophy.

By

SVEN BRANDT, Aarhus.

In 1923 Stern has described a congenital condition consisting of restricted mobility of a number of joints which are fixed in extended or flexed positions. He gave this condition the name of arthrogryposis (*curved joints*) multiplex congenita (a. m. c.). The muscles are atrophic or insufficiently developed, the joints, especially the elbows and knees, therefore appear fusiformly swollen, while the osseous system is complete and sensibility and reflexes are normal.

This striking and severely disabling condition was, however, wellknown among orthopedists and surgeons before Stern. Cases have been described in German medical periodicals as »Multiple kongenitale Kontrakturen» (Wunsch 1901, Magnus 1903, Ewald 1907, Hohmann, Tobler 1907, Schulz 1924) or as »Multiple kongenitale Gelenkstarre» (Schulte 1924, Valentin 1937). Also among French orthopedists the affection has been known for a long time. According to Valentin, Guérin has given the first description in 1880. In 1913 Rocher collected 26 cases from the literature under the designation of *rigidités articulaires multiples congénitales*. Particularly from Russia several reports have appeared in recent years, unfortunately inaccessible to the author (Avanitopulo, Bogdanow, Churgin).

Varying theories on the cause of the affection have led to still a couple of names: amyoplasia congenita (Sheldon) and

myodystrophia deformans foetalis (MIDDLETON). In Denmark the affection has not been described before. BERNTSEN, however, in 1930 has reported 3 cases of manus vara congenita, which resemble this disease.

Symptoms.

In typical cases where all four extremities are deformed the child has a characteristic appearance, which has been aptly compared to that of a wooden doll: the arms are kept rotated inward in the shoulder joints, extended in the elbows, pronated with the backs of the hands looking forward. The hands are strongly flexed and most often also deviating somewhat ulnarly (manus ulno-palmaris), the carpus and the fingers being compressed from side to side and the fingers flexed in a more or less claw-like manner. The legs are kept flexed and rotated outward in the hips, extended or hyperextended in the knees (the children walk *as if on stilts* (Heijbroek)), and the feet are in a pronounced varus position, so that in the most severe cases the child stands on the backs of its feet.

Complete ankylosis of the joints is rare. Passive movements can almost always be performed to some, though often to a very limited, extent. It is characteristic that the movement is easy until a firm unelastic hindrance is encountered. This, according to PRICE, is capsular or ligamentar and not muscular. A more springy resistance is, however, met with in some cases, so that the limb is seen to rebound to its position of predilection, after the movement has ceased (Woringer, Ewald 1907). The active mobility is, however, much more restricted, though this depends somewhat on the direction of the movement. E. g. the patients may be fairly able to flex the wrist from its ulno-palmar position, sometimes even more than is physiological, while they cannot move the hand in a dorsal direction, not even till the wrist is straight. This is because of a severe atrophy or aplasia of certain muscle groups. The deltoids and deep shoulder muscles, the flexors of the arms and thighs together with the extensors of the lower arms in particular are involved.

The deformities may involve the upper extremities only,

less frequently the lower extremities only. As a rule the affection is symmetrical, though occasionally differing in degree on the two sides. In some cases only one side is involved.

Sometimes the joints are fixed in other positions. Thus, the knees may be fixed in flexion (Magnus, Heijbroek, Lewin, Middleton, Moncrieff), the wrist joints in dorsiflexion and the elbows in a more or less pronounced flexion. Pes planovalgus is seen combined with pes equinovarus on the opposite side.

Luxation of the hip joint is often present, and subluxations of the elbows, knees and thumbs are common.

Rarer symptoms are: a short neck and elevated or atrophic scapulæ (Magnus, Moncrieff, Schanz), torticollis (Cook), kyphosis (Heijbroek), scoliosis (Middleton). In a single case there was restricted mobility in the mandibular joints (Schanz). Web formations between the fingers or in the poples (in connection with fixation in flexion) are seen now and then (Berntsen). The skull may be deformed with flat occiput and bulging temples, as in Schanz's case.

In a number of cases Rosenkranz found a series of other deformities, among others: polydactylia, amniotic constriction of the fingers, finger atrophy or hypertrophy, herniæ, genital deformities, anal atresia, hydrocephalus etc.

The skeleton is always complete with the one exception that the patella may be absent in cases with marked hyperextension of the knee (genu recurvatum) (FAIRBANK, MARCONI, SCHULZ). The joint surfaces of the bones are, however, often somewhat deformed: bent in abnormal directions or incomplete.

The subcutaneous tissue is often very abundant, thickened, especially in the distal parts of the extremities, their circumference being greatest distally (COMBY, HELJBROEK, SHELDON).

The intellect of these children is unimpaired. A couple of exceptions bear out the rule (MIDDLETON, COOK, whose patient was also a Mongolian idiot). It is often surprising to see how capably these patients adapt themselves to the claims of social life, even when untreated, if only the restricted mobility of the joints and their position are not wholly disabling (EWALD 1907).

The birth of the child is often influenced by the deformities. Many of these children are born with a breech presentation (Comby, Hohmann, Schanz, Schulz, Sheldon). With head presentation the flexion contractures of the hips have lead to fracture of both thigh bones (Heljbroek). Several authors have noticed that amniotic fluid was extremely scanty and ascribé to this fact a certain etiological significance. Some mothers have complained of foetal movements being very weak or absent (Scarlini, Worlinger), whereas others have found them strikingly marked and painful (Schanz).

ROCHER found the affection somewhat more frequent in boys (15 in 22). This hardly holds true. Among 48 cases accessible the author found 25 boys and 22 girls.

Pathologic-anatomical examinations of the musculature and the nervous system of children with this affection have been carried out only in a few cases. The cause — or possibly causes — of this clinical picture is, therefore, still obscure. Theories are, however, legio. Before these are discussed, the author shall report the history and the results of pathologic-anatomical examinations of a case, completely resembling a. m. c. as described in the available literature.

Case history.

Boy, admitted 3 weeks old into the pediatric department of Aarhus Kommunehospital (Case record 296/44).

Parents healthy, mother 32 years old, father 43. Countrypeople.

The youngest brother of the mother feeble-minded and born with a hemiplegia. No further deformities or nervous diseases in the family.

First-born. Later his mother has born a healthy child. Easy delivery at term after normal pregnancy. The quantity of amniotic fluid was estimated to be normal. Weight at birth 3 200 g.

Since birth the child has eagerly reached for the breast when put to it, but has been unable to suck and consequently has had practically no nutrition. Attempts at bottle feeding have also had to be given up. The stools have been scanty, dark and greenish. He has severe congenital malformations of the extremities. Twitchings, convulsions or choking spells have not been observed. He has lost considerably in weight, the skin is dry and scaly, and he looks miserable.

At the time of admission he weighs 2630 g. The skin is every-

where flabby, folded over the underlying structures, and subcutaneous fat is totally absent. The epidermis is dry, desquamating with scattered sudaminous spots, in places leathery and slightly glossy. The deformities can be seen from the accompanying photographs.

The arms are kept rotated inward with the backs of the hands turned forward and both hands in 45° volar flexion and slightly devi-





Fig. 1.

Fig. 2.

ating ulnarly. They cannot be extended passively, but flexed passively to a further extent so that the fingers can be placed against the flexor side of the lower arms. The thumb is fixed in the opposed position making the hand look slender and long. The elbows can be flexed passively 70° from full extension. Pro- and supination is only possible to a few degrees, so that the pronated position is practically fixed. Abduction in the shoulder joint with the scapula fixed is only possible to 45 degrees and rotation to a few degrees. The restricted joint mobility is, it must be supposed, in part of muscular origin — the mm deltoidei and latissimi dorsi, e. g., are very short and tight —, but mostly it is arthrogenic. The articular changes in the upper extremities are on the whole symmetrical, only the pronated position is less pronounced in the right arm, where supination can be performed to a slightly greater extent than

in the left arm. Everywhere in the upper extremities there is pronounced muscle atrophy, especially in the shoulder regions and the proximal parts of the arms. The biceps muscle is felt like a string of pencil thickness. In the lower arms the muscles appear somewhat more voluminous, but the evaluation is made difficult by a thickened subcutis of a doughyoedematous consistence. The active mobility of the upper extremities is very small, only rocking movements being possible, especially in the shoulder and finger joints.

The lower left extremity is kept in 30° abduction in the hip joint, so that the patella is facing laterally and forward. Passive flexion of the left knee is reduced to 30 or 40°. The left hip can be flexed 30° and rotated 10 or 15° and abducted 60°. The left foot is turned inward in the ankle joint so that the plantar surface of the heel is facing medially. Further, the foot is bent so that the toes point medially and the back of the foot points forward (pes equinovarus). The right hip resembles the left one completely. The right knee is overextended about 30° (genu recurvatum) and can be overextended a further 10°, whereas flexion is quite out of the question. The patella is present. The mobility of the right ankle joint is somewhat restricted, the toes a little bent, but apart from this no characteristic deformity is seen here. The muscular atrophy of the lower extremities equals that of the upper extremities in severity, both in the buttocks, thighs and legs, and the active mobility is practically nil. The tendon reflexes cannot be evaluated on account of the joint stiffness. The plantar reflexes are normal. Muscle fibrillations are not seen, nor are they revealed in the electrocardiogram, which shows no certain pathological changes. The trunk: practically no dorsal muscles are to be felt, and there is also severe atrophy of the cervical muscles. The child is in opisthotonus. This may be due to the fact that the dorsal muscles left, as for that matter all the muscles left, are rigidly hypertonic, but more probably it is the result of contracture with restricted joint mobility similar to that of the extremities (relative preponderance of the extensor muscles of the spine on account of still more weakness of flexor muscles). Also the facial muscles are very atrophic. This is specially apparent in the orbicularis oris and risorius muscles. The mouth can, therefore, hardly be closed, the lips are retracted, the gums are uncovered, and the canine region of the lower jaw is strongly prominent. The lower jaw is slightly wry, its left half being on a higher level than the right half.

The ocular movements are well coordinated, and the child is able to fix objects. There is no paresis of the velum palatinum or the tongue. The skull is firm, natural, the size of the anterior fontanel equals two finger pads. The general examination discloses no further anomalies except hypospadia. Roentgenograms of the bones of the extremities show no osseous defects. Immediately above the calcification zone in the diaphyses of

the long bones there is a rarification of the structure, and the calcification zone itself appears as if drawn with a pencil, that is to say: slightly intensified. It bears certain resemblance to osteochondritis syphilitica, and is possibly due to an atrophic condition of the bone.» (Signed Flemming Møller, who has been kind enough to look over the roentgenograms.)

Electrical irritation of the n. radialis and the n. peroneus with a galvanic current produces lightning contractions on cathode closing (6 railliampères) but no reaction on cathode opening and anode opening. N. radialis responds to 9 milliampères on anode closing, n. peroneus does not react. The spinal fluid shows a normal cell count and normal protein values. Fasting blood sugar level 98—85—80 mg p. c. Hemoglobin 92 p. c. Urine: no protein, no sugar. Excretion of creatinine per day: 2.5 mg (not pathologic for the age). Biopsy of the quadriceps muscle: v. i. Neurologist (Dr M. Lund) confirms the examination and subscribes to our diagnosis: arthrogryposis multiplex congenita.

Course: The child grew steadily worse during its stay in hospital. The food had to be *pumped* into its mouth by pressure on the nipple of the bottle. Swallowing was normal. He fixed objects and followed the staff of the department with his gaze. Any closer evaluation of the mental development of the child was, of course, out of the question, but

it did not impress as being feeble-minded.

Death occurred one month after admission, when the child was 7 weeks old.

Autopsy revealed no anomalies of the internal organs. The brain and the spinal cord was fixed with a 10 % aqueous solution of formaldehyde for the purpose of histological examination by professor Einarson.

Inadvertently no sample of muscular tissue was taken during autopsy, but fortunately biopsy of the right quadriceps muscle had been made.

Microscopical Examination.

Tissue from the quadriceps muscle:

The present, mostly longitudinally cut, preparation shows very severe changes. Besides a considerable increase of interfascicular connective-tissue an extreme atrophy of the muscle cells is seen in most places. The muscle cells therefore appear as areas rich in nuclei, bits of narrow threads with preserved striation being found only in a few places (Fig. 3). In other places, where the atrophy is not yet maximal, bundles of narrow muscle fibrils with well-preserved striation are to be seen (Fig. 4). Both in these, as in the other muscle fibrils of more normal calibre (Fig. 4),

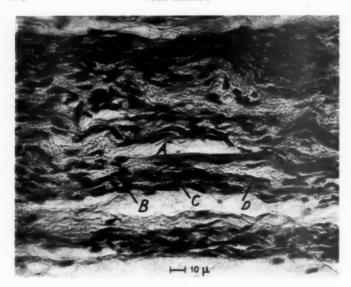


Fig. 3. Tissue from m. quadriceps. Hematoxylin-eosin-preparation ($\times 420$). The muscle tissue has almost disappeared. At A, B, C and D remnants of muscle fibres with preserved cross-striation are seen. Pronounced nuclear proliferation and increase of connective-tissue.

a considerable increase in hypolemmal nuclei is seen. In a very few places where the preparation has been transversely cut, there is a suggestion of the intermingled areolar distribution of atrophic and normal fibrils, characteristic of spinal muscle atrophy. On the whole the musculature is not the site of degenerative changes. In some places, however, both hyalination and vacuolation is seen with transparent droplets in the protoplasm and no striation. These changes may, however, be artefacts. There are no inflammatory infiltrations and no vascular changes.

In the central nervous system pronounced degenerative changes of the peripheral motor neurone are to be found.

The spinal cord (Fig. 5, 6 and 7) (preparations stained with gallocyanin after Einarson): the anterior horns throughout the cord show changes corresponding to Nissl's »profound cell change» with granular, finely or coarsely vacuolar degeneration leading

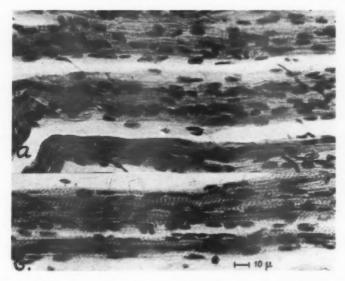


Fig. 4. Tissue from m. quadriceps. Hematoxylin-eosin-preparation (\times 420). Above: muscle fibres of nearly normal thickness (20—30 μ), but with a very pronounced increase in the number of hypolemmal nuclei. Below: atrophic muscle fibres with well-preserved cross-striation. Considerable increase in the number of hypolemmal nuclei.

to total disappearance of the motor cells of the anterior horns and leaving empty spaces in the tissue. Add to this extreme chromophily and cell sclerosis with vacuolation. All degrees of pathological change are represented. In all cell groups, there remain, however, scattered still normal nerve cells, specially in the antero-medial cell group (i. e. that innervating the long dorsal muscles). Practically only the motor cells of the anterior horns are involved. The cells of the lateral horns and Clark's column are nearly all of them well-preserved and normal. By fat-staining methods products of lipoid disintegration are nowhere demonstrated. In preparations stained by Spielmeyer's method there is no demyelination of the white matter of the spinal cord, whereas the pyramidal tracts and a few other tracts are still incompletely myelinated, in close accordance with the age of the child.

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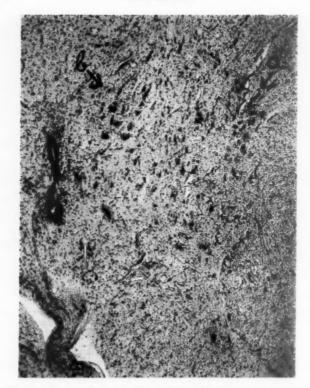


Fig. 5. Thoracic part of the spinal cord. Left half of the grey matter. Gallocyanin-preparation (× 106). The motor cells of the anterior horn mostly disintegrated. In the lateral horn (a) and Clark's column (b), respectively, the cells are well-preserved.

The medulla oblongata and the mesencephalon: the nucleus spinalis nervi accessorii is clearly involved. The left facial nucleus is severely affected, while the right facial nucleus is far less damaged. The nucleus supraspinalis, the nucleus ambiguus and the nucleus nervi hypoglossi are for the most part normal. The nuclei of the ocular muscles are normal.

Other parts of the central nervous system: in the nucleus lenticularis besides normal ones there are also several relatively

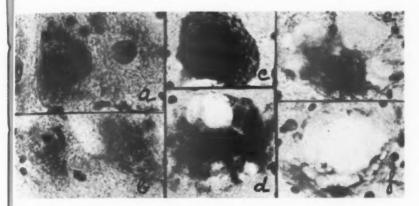


Fig. 6. Anterior horn cells from the lumbar part of the spinal cord. Gallocyanin-preparation (\times 600). a: normal chromoneutral and chromophobe cells from the antero-medial cell group. b: nearly normal cells from the posterior part of the antero-medial cell group. The nuclear membrane indistinct. c: pronounced degeneration with fine vacuolation and nuclear pyknosis. d: a very typical strongly vacuolated cell with hyperchromatic cytoplasm from the antero-lateral cell group. e: vacuolar degeneration and incipient nuclear pyknosis. f: empty space in the tissue following almost total disappearance of anterior horn cell.

slightly degenerated cells (vacuolation, hyperchromasia, nuclear pyknosis), this is especially the case in the globus pallidus. The nucleus caudatus is mostly normal and the thalamus is completely normal. The cortex cerebri is predominantly normal. It should be specially stressed that the giant cells of Betz in the central region are mostly well-preserved, though here and there a few are found, which show slight vacuolation. They are mostly chromophobe.

In the centrum semiovale and the capsula interna entirely normal conditions are met. There is no demyelination, no occurrence of fat or other products of disintegration. The glial tissue shows normal conditions, though both the pericellular oligodendroglia of the cortex and the interfascicular oligoglia are swollen to a slight degree, which must, however, be considered an agonal change.

In the cerebellum conditions are judged entirely normal.

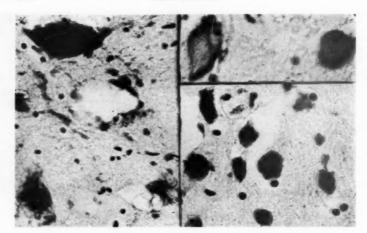


Fig. 7. Left: anterior horn cells from the cervical cord. Gallocyanin stain (\times 420). An extremely chromophile cell, turning into sclerosis, together with profoundly changed cells with vacuolation and nuclear pyknosis, besides an nearly empty space in the tissue left by a disappeared cell. Top right: normal, very characteristic cells from Clark's column in the thoracic cord. Gallocyanin stain (\times 600). The nucleus is excentrically situated. In the interior of the cell the Nissl substance looks very fine-grained, almost dusty, while there is an accumulation of denser, more intensely stained substance in the periphery of the cell. Bottom right: normal cells from the lateral horn in the thoracic cord. Gallocyanin stain (\times 600). The cells are small and alternatingly arkyo-gryochromatic, more lightly stained, and arkyo-stichochromatic, more darkly stained.

The connective tissue and vascular apparatus of the central nervous system show nothing abnormal, and infiltrations are found nowhere.

Histological diagnosis: muscle atrophy on account of degenerative changes in the spinal cord (Einarson).

The case described above is, then, one of degeneration of the peripheral motor neurone, beginning in foetal life and taking a rapid course. Pathogenetically the affection would seem to be related to the malignant form of amyotonia congenita, which is in reality a congenital form of Werdnig-Hoffmann's spinal muscle atrophy. Clinically, however, it presents a widely different picture. In amyotonia congenita the child is atonic, hyperflexible and hypokinetic. Admittedly, contractures are seen in Werdnig-

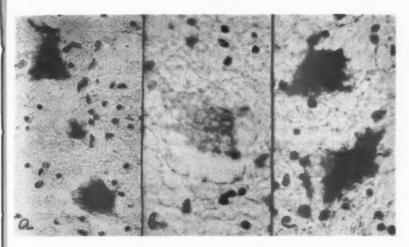


Fig. 8. Motor cells from the anterior horns (Gallocyanin stain). a: two nearly normal, chromophile cells from the antero-lateral cell group of the cervical cord (\times 400). b: a typical, complete cell shadow from the lumbar cord (\times 600). c: two selerotic and also strongly vacuolated cells from the antero-lateral cell group of the lumbar cord (\times 600).

Hoffmann's disease, but as a rule they develop later in its course and are predominantly muscular, consequent upon shrinking of the paretic muscles. It is very probable that the joint stiffness in arthrogryposis multiplex congenita has come about in a different way, as inter al. Sheldon has supposed: if the foetus for some reason or other is unable to bend or stretch its joints (it may be on account of partial muscle aplasia, oligohydramnios or — as in our case — muscle atrophy) the passive apparatus of motion with its joint capsules and ligaments is not developed so as to provide the necessary freedom of motion. The joint capsules remain undeveloped and tight and allow only of minimal movements.

If, however, the degeneration of the peripheral neurone does not start till at a later stage of foetal life, when the foetus through lively kicking and floundering has developed its passive apparatus of motion to a normal degree, we may encounter the more familiar picture of amyotonia congenita.

It is very interesting that on going through the literature on Werdnig-Hoffmann's disease and amyotonia congenita one does actually encounter cases, which bear a strong clinical resemblance to arthrogryposis multiplex congenita (Karström and Wohlfart 1939 (case 5) and Lehoczky). Also a couple of cases reported as dystrophia musculorum progressiva congenita resemble ours clinically (Howard, Schlivek), and a single author (Scarzella) finds disappearance and atrophy of the motor cells of the anterior horns of the spinal cord as in our case (but he calls his foetal muscle dystrophy).

Histological examination of the spinal cord has been performed in only one case of arthrogryposis multiplex congenita (Price). That author found *shrunken and degenerated* ganglion cells in both anterior and posterior horns, degenerative changes with glial proliferation in the white matter, slight dilatation of the canalis centralis and small interstices filled with blood-vessels in the cord tissue. The meninges were the site of chronic inflammation. Price believes the disease to be due to infection in the amnion cavity having penetrated into the nervous system at a time when the neural tube was only partially closed.

MIDDLETON, who mentions Price's patient but despite that author's conclusion regards the disease as a myogenic dystrophy and calls it myodystrophia foetalis deformans, brings microphotographs of muscular tissue from Price's patient. He calls the changes dystrophic, but in the light of present knowledge in this field these pictures must be said to represent the most beautiful example to be imagined of a neurogenic atrophy.

It is specially interesting that ROBERTS has described a condition found in sheep, resembling a. m. c. and being a recessively linked hereditary disease, as is the case with Werdnig-Hoffmann's disease.

While it can, thus, be established as a fact that a foetal spinal muscle atrophy and for that matter probably also a foetal myogenic atrophy may lead to the clinical picture of arthrogryposis multiplex congenita, it can, however, not be claimed that those are the only causes. Thus, there have never been reports on familial cases of a.m.c., which might have been expected, had

there been a connection with Werdnig-Hoffmann's disease. In one case only (Heijbroek) the disease is reported to have been found in uniovular twins. One of the twins died immediately after birth. Like his brother he had club-feet, but Heijbroek had not an opportunity to examine if he shared his brother's other deformities. One also gets the impression from the literature that the condition of a.m.c. mostly remains practically stationary without progressing to sections of the muscle system, which are still relatively well-preserved.

It is, therefore, necessary to look for more causes of this peculiar disease. Sheldon has thought that it was a question of congenital aplasia of certain muscle groups, so that the preserved antagonists are acting alone. He, therefore, names the affection amyoplasia congenita.

Explanations as foetal rickets have probably only historical interest. Stern speaks of a foetal periarthritis and Price, as mentioned before, of an inflammation having penetrated into the nervous system from the amnion cavity. In most cases, however, the pregnancy is entirely uncomplicated and the mother completely well, and an explanation of that kind therefore extremely improbable.

Oligohydramnios has been found in a number of cases (Hohmann, Middleton-Fraser, Schanz, Schulz, Woringer). This is thought to lead to a cramping up of the foetus and to hamper its movements, which must, as already mentioned, be considered an important mechanical factor in developing articular surfaces, joint capsules and ligaments as well as muscles. This explanation has, probably unjustly, been rejected too categorically by some authors (Middleton, Comby). In some cases, in which also other signs of "pressure" occur, it would seem reasonable to suppose some such condition to be the cause (vide e. g. Schanz).

The prognosis of a. m. c. is, of course, the worst possible in the cases in which the cause is a rapidly progressing degenerative process. In the cases stationary from birth, in which the cause is probably a different one, the results of orthopedic treatment in due time are, in the opinion of some authors (CAMPBELL, COMBY),

so good that a number of patients can be helped to find a tolerably good place in society. The condition of the muscles determines whether improvement of mobility is attained.

The treatment is orthopedic and consists of repeated redressements, passive movements, temporary fixation in over-corrected positions and correcting operations (tenotomies, osteotomies etc.).

The diagnosis seldom presents difficulties. It would undoubtedly be of some importance in judging the chances of effectivity of treatment, if an evaluation of the state of the muscles was possible. By muscle biopsy it will without doubt in a number of cases be possible to learn, whether the cause of a particular case is a spinal or perhaps a myogenic progressive muscle atrophy. If normal muscle tissue were found, it might be expected that orthopedic treatment would be worth while.

The disease is described as rare, but the present author is inclined to think that it is more frequent than generally supposed among pediatricians and neurologists, and that a number of patients might be found in orthopedic departments.

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PROCEEDINGS OF PEDIATRIC SOCIETIES

Proceedings of the Norwegian Pediatric Society.

Meeting in the Pediatric Clinic of the University, Rikshospitalet, Oslo, February 6th, 1947. Report by the secretary, Dr. Arne Njå.

Gunnar Nyhus: Peroneal Muscular Atrophy in One-Egged Twins.

The two main groups of progressive muscular atrophy were mentioned in the introduction. 1: The spinal neuropathic muscular atrophies and 2: The primary myopathic atrophies.

The female twins, 4 years old, were treated in the Pediatric Clinic of the University in autumn 1946. During the last 1 1/2 years prior to admission a typical picture of peroneal muscular atrophy developed with identical findings in the two twins. The differential diagnosis against other heredopathies was discussed. In this connection the very rare, distal, atypical type of dystrophia musculorum progressiva is very interesting because a sister and a brother of the twins' mother suffered from the pseudohypertrophic, infantile type of dystrophia musculorum progressiva. The result of the biopsy should be decisive for the diagnosis, therefore. However, the biopsy was not convincing, although as a whole indicating a spinal muscular atrophy as seen in the peroneal muscular atrophy. On the contrary, if the twins were suffering from an atypical, distal type of dystrophia musculorum progressiva, an explanation for this would be very difficult since a sister and a brother of their mother were suffering from the pseudohypertrophic, infantile form, in which the atrophy starts in the muscles of the pelvis and the shoulder girdle. In dystrophia musculorum progressiva the same form of the disease is inherited in the same family. The lecturer concluded that — based upon the symptomatology and the muscle biopsy — the case must be regarded as one of peroneal muscular atrophy, but that only the further course will establish the diagnosis definitely.

Knut Lunde: Atresia Oesophagi Congenita with Oesophago-Tracheal Fistula.

After having remarked briefly upon the incidence of the disease, a patient from the University Maternity Hospital was recorded, presenting the characteristic picture of the disease: Vomiting, cough, restlessness,

cyanosis and respiratory stop on the slightest attempt at feeding — recovered in a few minutes — and mucous secretion from the mouth between the seizures. Increasing dehydration and death on the fifth day of life.

Roentgenograms, a photograph and an autopsy specimen were demonstrated. The patient also presented an anomaly of the fingers and of the urinary tract.

The embryological data explaining the possibilities of development of different anomalies in the oesophagus, and the attempt at treatment which has been made, were reported on in brief.

Lars Gram: Preventive Inoculation against Whooping Cough.

It is stated that whooping cough is one of the most dangerous of the children's diseases, with a high mortality rate, especially in early infancy.

The means available for estimating the effect of the inoculation was reviewed based upon recent and earlier publications. They include investigations of mortality and morbidity, studies of the immuno-biological reactions in different age groups after inoculation, of the complement fixation test, of the agglutination test and of intradermal tests with H. pertussis antigen.

The different varieties of whooping cough vaccines were accounted for: The usual formol-killed vaccine, the alum precipitated vaccine, possibly combined with diphtheria anatoxin and tetanus toxoid.

The importance of using new-isolated Phase I strains of H. pertussis for making the vaccines was emphasized.

The dose and mode of administration were mentioned. Good results have been obtained with Danish formol-killed vaccine with 10 000 millions bacilli per mil. 0.5—0.7—1.0 mil. are injected with 3—4 days' interval. American investigators recommend far larger doses. They use vaccines containing 15 000—20 000 millions bacilli per mil. and inject 1—2 mils. in three doses with an interval of one month between the doses.

The main directions for use of the vaccine were discussed. It was emphasized that when risk of infection is present vaccine may be beneficial and should be administered to infants before the age of 6 months, even as early as in the 2nd to 4th week. It is also indicated to inoculate the mother in the last month of pregnancy, but even then the baby within 6 months of age.

The conclusion was drawn that an ordinary, good, formol-killed vaccine is valuable during epidemics because the inoculation immunity may precede a more permanent immunity from a mild or sub-clinical H. pertussis infection. For the mere purpose of prophylactic inoculation the alum precipitated vaccines may be more suitable, although they may cause more pronounced fever reactions and occasionally abscesses. The inoculation period here runs over several months, the immunity lasting

for at least six months. To obtain a permanent protection the inoculation should be repeated every year with one dose.

Discussion: — Aaser, Stoltenberg, Sundal, Collett, Smith, Ødegård, Åser.

Aaser stated that he had listened to the lecture with great interest. He knew that the vaccines produced at the Institute of Public Health had been rather weak, but stated that it now has been increased to twice its former strength. Everything is now done to at all times provide potent strains for the production of vaccine. On application to the Institute, physicians will on short notice be supplied with whooping cough inoculation plates for use in their practice.

Meeting in the Pediatric Clinic of the University, Rikshospitalet, Oslo, March 3rd, 1947.

Roald Rinvik: Hospital Conditions for Children in Oslo and Aker,

Rinvik pointed out the present, desperate conditions as to hospital space for children. He stressed that something should be done to improve these conditions and indicated that in this case the Norwegian Pediatric Society ought to take the initiative.

Discussion: - Sundal, Stoltenberg, Smith, Njå.

Alf Ødegård: Demonstration of Pellagra in a Girl Aged 9 Years.

The patient has always eaten very little. The anorexia has increased during the last year. From July 1946 unsteady gait, stumbling easily. Hearing impaired, skin lesion on elbows and knees. Vitamin B_1 treatment only temporary effect. Exacerbation in February 1947.

Physical examination March 20th, 1947: Girl, 9 years old, skinny, delicate. Spoken voice just audible ad concham. Psychically normal. Slight, brownish-red hyperkeratoses on knees and elbows. Neurological examination besides the impaired hearing revealed a slightly deficient tactile sensation in fingers and toes, no demonstrable paresis. The gait was slightly atactic. Romberg's sign present. All tendon reflexes missing. Examination of the spinal fluid revealed strongly positive protein tests, but the number of cells was not increased.

The diagnosis of pellagra was made from the history, the skin lesions and the signs and symptoms of polyneuritis. Neuritis of the auditory nerve, as far as we know, has not previously been described in pellagra.

The changes in the spinal fluid may be due to the polyneuritis.

The case is almost identical with another one which recently has been treated in the clinic.

Alf Ødegård: Edema, Hypoproteinemia and Fatty Liver in Two Infants.

Hypoproteinemic edemas may be caused by an insufficient intake of protein (inanition, chronic intestinal disease), or it may be due to a defective synthesis of serum proteins (liver disease). Salomonsen and also McQuarrie, Thompson and Bell have previously described cases in children. In McQuarrie's cases a peculiar atrophy of the liver cells was found.

Two personal cases, on which autopsy was performed, are mentioned.

Case 1. A boy, 3 months old, thriving poorly from birth. Vomiting, development of general edemas.

Physical examination April 24th, 1946: Skinny, dystrophic, with general edema. Weight 4 600 g. (Birth weight 4 500 g). Physical examination otherwise nil. The patient died 14 days after admission to the hospital. Autopsy revealed a somewhat enlarged, yellowish, pale liver, weighing 330 gm. The liver markings were effaced. Microscopy revealed a marked and extensive fatty degeneration. The pancreas was slightly fibrosed, otherwise normal.

Case 2. A girl, 3 months old (two-egged twin), thriving poorly from birth. Vomiting, subsequent development of general edemas.

Physical examination April 4th, 1945: Weight 3 300 g. (Birth weight 2 200 g.) Marked edema, especially of the dorsal aspects of feet and hands. Physical examination otherwise nil. The patient died ten days after admission to the hospital. Autopsy revealed a yellowish, pale liver, weighing 150 g. The liver markings were effaced. Microscopy showed a marked fatty degeneration of the liver cells, which were completely vacuolated.

The first patient had a serum protein content of 3.53 mg per cent (alb. 1.38, glob. 2.15). The other patient had a total serum protein content of 2.5 mg per cent (alb. 1.9, glob. 0.6). Both were anemic, the hemoglobin content 50 and 45 per cent respectively.

The first patient had a slightly increased icterus index of 23. The serologic and tuberculin tests were negative in both.

The Rhesus factor was determined in the first patient. The mother was Rh + and the child $Rh \div$. Thus there was no indication of erythroblastosis or hydrops congenitus with hypoproteinemia as described by Salomonsen.

Hypoproteinemia and edema are described in fibrosis of the pancreas by *Glanzmann* and others. This was not demonstrable in our cases. However, the pancreas was not examined specially with a view to possible fibrosis. The anemia in these cases cannot be regarded as the cause of the fatty degeneration in the liver and of the subsequent hypoproteinemia, but may be regarded as a co-ordinated symptom to the existing disease. Litwak and Gruber maintain that hypoproteinemia alone may damage the liver and in this way interfere with the synthesis of the serum proteins, thus causing a circulus vitiosus. This they suppose may be broken by intravenous administration of plasma protein.

A definite cause of this condition cannot be given. It is suggested, therefore, that a more close examination of the pancreas should be made in similar cases.

Arne Njā: Chronic, Non-Familial Hemolytic Anemia in Infants. (To be published in Acta Pædiatrica.)

To the meeting May 8th 1947, were invitated the members of the Norwegian Psychological Society.

Alex. Brinchmann: The Negativism in Infants and Children from Pediatric and from Psychological Point of View.

DISCUSSION: Åse Gruda Skard, Stoltenberg, Brinchmann, Nic Waal, Åse Gruda Skard, Hedvig Trætteberg, Stoltenberg, Brinchmann, Nic Waal, Åse Gruda Skard.

